

COMPETITIVE PROBLEMS IN THE PHARMACEUTICAL DRUG INDUSTRY

HEARING

BEFORE THE

SUBCOMMITTEE ON ANTITRUST,
MONOPOLIES AND BUSINESS RIGHTS

OF THE

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

ONE HUNDREDTH CONGRESS

FIRST SESSION

ON

THE GENERIC DRUG INDUSTRY AND ITS CONCERNS WITH RESPECT TO
COMPETITION FROM THE BRAND NAME MANUFACTURERS

OCTOBER 21, 1987

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COMPETITIVE PROBLEMS IN THE PHARMACEUTICAL DRUG INDUSTRY

WEDNESDAY, OCTOBER 21, 1987

U.S. SENATE,
SUBCOMMITTEE ON ANTITRUST,
MONOPOLIES AND BUSINESS RIGHTS,
COMMITTEE ON THE JUDICIARY,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:53 a.m., in room SD-226, Dirksen Senate Office Building, Hon. Howard Metzenbaum, chairman of the subcommittee, presiding.

Present: Senators Metzenbaum, Thurmond, Specter, and DeConcini.

OPENING STATEMENT OF SENATOR METZENBAUM

Senator METZENBAUM. The Chair wants to apologize for being late, but there was a roll call vote on the floor of the Senate at about 9:35 and so I had to get over to it.

As we open these hearings, the Chair has a true sense of concern about the confusion that exists about generic drugs. The last thing a sick person needs to worry about is medical bills.

In 1985, Americans spent about \$28.5 billion on drugs, 77 percent of which was paid directly by consumers. Every taxpayer, even if he or she is never ill, still helps pay for the high cost of prescription drugs through State and federal contributions to Medicare and Medicaid.

A good way to cut medical bills is to reduce the cost of prescription drugs. FDA-approved generic drug equivalents help do just that. My staff in Ohio conducted a price survey of seven frequently prescribed drugs, both brand names and their approved generic equivalents.

The survey shows that approved generic equivalents offer major savings. For example, in Cleveland a person with diabetes whose doctor has prescribed Diabinese could save up to 79 percent by using the approved generic equivalent. A person living in Columbus whose doctor prescribes Valium could save up to 91 percent by taking the approved generic equivalent.

One only has to look at this chart to see the kind of savings that are possible. A product called Indocin for arthritis, \$35.98—these are the prices from Revco Drug Store in Columbus, Ohio, for a quantity of 100—a savings by using the generic of \$6.00. Aldomet/Methyldopa for high blood pressure, \$43.01; cost of generic is \$16.90, for a savings of 61 percent.

Diabinese/Chlorpropamide for diabetes, \$38.26, a savings of 89 percent is available by buying the generic at \$4.34. Here, Valium/

Diazepam, antianxiety tranquilizer, \$31.94, a savings of 91 percent available by buying the generic at \$2.84. Lasix/Furosemide, a savings of 67 percent is available by buying generic. And with Inderal/Propranolol for high blood pressure, a savings of 78 percent is available by buying the generic.

I think that tells the story in a nutshell of the kinds of savings that are possible by using generics. According to the best available evidence obtained from state-of-the-art technology, experts inside and outside the Food and Drug Administration assure me that generic drugs approved by the FDA as equivalent are the same as brand name drugs.

Furthermore, the FDA advises me that there has never been a documented, verified case of a therapeutic failure caused by a generic product that has been approved by the FDA and evaluated as therapeutically equivalent. So why would anyone pay more for the same medicine? It does not make any sense, and everyone knows it.

The brand name drug companies know it, too, but instead of competing head-to-head with approved generic equivalents on price, some companies have embarked on an all-out effort to scare consumers, doctors, pharmacists, and State formulary authorities from using, prescribing and dispensing generic drugs.

Let me just describe a few of the tactics some pharmaceutical companies have used in the last three years: sending letters to pharmacists implying that the pharmacist will be subject to liability for prescribing generic drugs which the letter claims are inferior; sending letters to doctors warning that unless they insist on the brand name drug for their patients, their patients' health and welfare will suffer; paying so-called experts to tour the country and make speeches warning of the dangers of generic drugs; funding institutes and foundations to report to the public on alleged problems with generic drugs; running hundreds of advertisements in medical journals stressing the need to insist that prescriptions be filled with only brand name drugs; presenting scientifically unsound studies to State authorities to suggest that brand name drugs are superior to generics; funding studies that falsely suggest that brand name drugs are cheaper than generics. One would not get that impression by looking at these charts.

By raising doubts about the safety and effectiveness of approved generic equivalents, these companies must hope that doctors, pharmacists and patients will fear approved generic equivalents and rely exclusively on higher priced brand names.

Today, we invited two companies that have been involved in anti-generic activity, Ayerst Laboratories and Pfizer Pharmaceuticals, to appear before the subcommittee. They have each declined to testify. Why?

Despite their refusal to appear today, the subcommittee intends to pursue this matter and I will be discussing throughout the hearing the activities of these two companies. When pharmaceutical companies undertake a campaign to mislead, frighten and confuse the American public, they must be held accountable. When they act to raise medical bills, particularly for the elderly, they must be held accountable. When they drive up Federal expenditures for Medicare and Medicaid, they must be held accountable.

I can assure those in the pharmaceutical industry, including Ayerst and Pfizer, that persist in unfair competition that the subcommittee intends to pursue this matter fully.

The subcommittee does not appreciate—yes, I think I would go further and say the subcommittee resents the failure of Ayerst and Pfizer to appear before this subcommittee, and the Chair at its own leisure will decide whether or not subpoenas will be issued for their appearance.

Our first panel is Dr. Jere E. Goyan, dean, University of California at San Francisco School of Pharmacy, San Francisco; and Rinaldo V. DeNuzzo, professor, Albany College of Pharmacy of Union University, and pharmacy consultant for the New York State Department of Health, Albany, NY.

I want to say how pleased I am that Dr. Frank Young, Commissioner at the Food and Drug Administration, is with us. On a protocol basis, it would be quite usual to ask him to speak first. He is prepared to listen to the other witnesses and to appear at a later point in the hearing so that he may be in a position to respond to the committee's questions concerning such matters as are testified earlier in the hearing, and we are very grateful to him for his cooperation with the subcommittee.

Dr. Goyan, we are happy to hear from you, sir. We hope that each of the witness' statements will be relatively modest in time. We normally have a 5-minute time limit. We will go a little bit longer, but not too long.

[Prepared statement follows:]

U.S. Senator Howard M.

METZENBAUM

of Ohio

Committees:
Judiciary
Labor and Human Resources
Energy and Natural Resources
Select Committee on Intelligence

Chairmanships:
Subcommittee on Antitrust
Subcommittee on Labor
Subcommittee on Energy
Regulation and Conservation

OPENING STATEMENT OF SENATOR HOWARD M. METZENBAUM
CONCERNING OVERSIGHT OF THE PHARMACEUTICAL INDUSTRY

THE LAST THING A SICK PERSON NEEDS TO WORRY ABOUT IS MEDICAL BILLS. IN 1985, AMERICANS SPENT ABOUT \$28.5 BILLION ON DRUGS -- 77% OF WHICH WAS PAID DIRECTLY BY CONSUMERS. EVERY TAXPAYER, EVEN IF HE OR SHE IS NEVER ILL, STILL HELPS PAY FOR THE HIGH COST OF PRESCRIPTION DRUGS THROUGH STATE AND FEDERAL CONTRIBUTIONS TO MEDICARE AND MEDICAID.

A GOOD WAY TO CUT MEDICAL BILLS IS TO REDUCE THE COST OF PRESCRIPTION DRUGS. F.D.A.-APPROVED GENERIC DRUG EQUIVALENTS HELP DO JUST THAT.

MY STAFF IN OHIO CONDUCTED A PRICE SURVEY OF SEVEN FREQUENTLY PRESCRIBED DRUGS -- BOTH BRAND NAMES AND THEIR APPROVED GENERIC EQUIVALENTS. THE SURVEY SHOWS THAT APPROVED GENERIC EQUIVALENTS OFFER MAJOR SAVINGS. FOR EXAMPLE, IN CLEVELAND, A PERSON WITH DIABETES, WHOSE DOCTOR HAS PRESCRIBED DIABINESE, COULD SAVE UP TO 79% BY USING THE APPROVED GENERIC EQUIVALENT. A PERSON LIVING IN COLUMBUS WHOSE DOCTOR PRESCRIBES VALIUM COULD SAVE UP TO 91% BY TAKING THE APPROVED GENERIC EQUIVALENT.

ACCORDING TO THE BEST AVAILABLE EVIDENCE OBTAINED FROM STATE-OF-THE-ART TECHNOLOGY, EXPERTS INSIDE AND OUTSIDE THE FOOD AND DRUG ADMINISTRATION ASSURE ME THAT GENERIC DRUGS APPROVED BY THE F.D.A. AS EQUIVALENT ARE THE SAME AS BRAND NAME DRUGS. FURTHERMORE, THE F.D.A. ADVISES ME THAT THERE HAS NEVER BEEN A DOCUMENTED, VERIFIED CASE OF A THERAPEUTIC FAILURE CAUSED BY A GENERIC PRODUCT THAT HAS BEEN APPROVED BY THE FDA AND EVALUATED AS THERAPEUTICALLY EQUIVALENT.

SO, WHY WOULD ANYONE PAY MORE FOR THE SAME MEDICINE? IT DOESN'T MAKE ANY SENSE -- AND EVERYONE KNOWS IT.

THE BRAND NAME DRUG COMPANIES KNOW IT TOO. BUT, INSTEAD OF COMPETING HEAD-TO-HEAD WITH APPROVED GENERIC EQUIVALENTS ON PRICE, SOME COMPANIES HAVE EMBARKED ON AN ALL-OUT EFFORT TO SCARE CONSUMERS, DOCTORS, PHARMACISTS, AND STATE FORMULARY AUTHORITIES FROM USING AND PRESCRIBING GENERIC DRUGS. LET ME JUST DESCRIBE A FEW OF THE TACTICS SOME PHARMACEUTICAL COMPANIES HAVE USED IN THE LAST 3 YEARS:

*SENDING LETTERS TO PHARMACISTS IMPLYING THAT THE PHARMACISTS WILL BE SUBJECT TO LIABILITY FOR PRESCRIBING GENERIC DRUGS WHICH THE LETTER CLAIMS ARE INFERIOR;

*SENDING LETTERS TO DOCTORS WARNING THAT UNLESS THEY INSIST ON THE BRAND NAME DRUG FOR THEIR PATIENTS, THEIR PATIENTS' HEALTH AND WELFARE WILL SUFFER;

*PAYING "EXPERTS" TO TOUR THE COUNTRY AND MAKE SPEECHES WARNING OF THE DANGERS OF GENERIC DRUGS;

*FUNDING INSTITUTES AND FOUNDATIONS TO REPORT TO THE PUBLIC ON ALLEGED "PROBLEMS" WITH GENERIC DRUGS;

*RUNNING HUNDREDS OF ADVERTISEMENTS IN MEDICAL JOURNALS STRESSING THE NEED TO INSIST THAT PRESCRIPTIONS BE FILLED WITH ONLY BRAND NAME DRUGS;

*PRESENTING SCIENTIFICALLY UNSOUND "STUDIES" TO STATE AUTHORITIES TO SUGGEST THAT BRAND NAME DRUGS ARE SUPERIOR TO GENERICS;

*FUNDING STUDIES THAT FALSELY SUGGEST THAT BRAND NAME DRUGS ARE CHEAPER THAN GENERICS;

BY RAISING DOUBT ABOUT THE SAFETY AND EFFECTIVENESS OF APPROVED GENERIC EQUIVALENTS, THESE COMPANIES MUST HOPE THAT DOCTORS, PHARMACISTS, AND PATIENTS WILL FEAR APPROVED GENERIC EQUIVALENTS AND RELY EXCLUSIVELY ON HIGHER PRICED BRAND NAMES.

TODAY WE INVITED TWO COMPANIES THAT HAVE BEEN INVOLVED IN ANTI-GENERIC ACTIVITY, AYERST LABORATORIES AND PFIZER PHARMACEUTICAL TO APPEAR BEFORE THE SUBCOMMITTEE. THEY HAVE EACH DECLINED TO TESTIFY.

DESPITE THEIR REFUSAL TO APPEAR TODAY, THE SUBCOMMITTEE INTENDS TO PURSUE THIS MATTER, AND I WILL BE DISCUSSING THROUGHOUT THE HEARING THE ACTIVITIES OF THESE TWO COMPANIES.

WHEN PHARMACEUTICAL COMPANIES UNDERTAKE A CAMPAIGN TO MISLEAD, FRIGHTEN AND CONFUSE THE AMERICAN PUBLIC, THEY MUST BE HELD ACCOUNTABLE. WHEN THEY ACT TO RAISE MEDICAL BILLS, PARTICULARLY FOR THE ELDERLY THEY MUST BE HELD ACCOUNTABLE. WHEN

THEY DRIVE UP FEDERAL EXPENDITURES FOR MEDICARE AND MEDICAID THEY MUST BE HELD ACCOUNTABLE.

I CAN ASSURE THOSE IN THE PHARMACEUTICAL INDUSTRY, INCLUDING AYERST AND PFIZER, THAT PERSIST IN UNFAIR COMPETITION, THAT THE SUBCOMMITTEE INTENDS TO PURSUE THIS MATTER FULLY.

The Right Medicine

(A Price Comparison Of Brand Name Drugs And Their F.D.A.-Approved Generic Equivalents)

Between October 6th and October 15th, 1987, staff at the Cincinnati, Cleveland, Columbus, and Toledo, Ohio offices of Senator Howard M. Metzenbaum conducted a price survey of certain brand name drugs and their F.D.A.-approved generic equivalents. The staff members recorded the price of 100 quantity of the following drugs at retail stores in their cities:

	<u>Drug</u>	<u>Dosage</u>	<u>Prescribed for</u>
1.	indocin (capsule) indomethacin	25 mg.	arthritis
2.	aldomet (tablet) methyldopa	500 mg.	high blood pressure
3.	diabinese (tablet) chlorpropamide	250 mg.	diabetes
4.	valium (tablet) diazepam	5 mg.	anti-anxiety tranquilizer
5.	lasix (tablet) furosemide	40 mg.	high blood pressure
6.	inaleral (tablet) propranolol	40 mg.	high blood pressure

According to the survey, Ohio patients whose doctors prescribe these drugs could realize substantial savings by purchasing the approved generic equivalent instead of the brand name drug. The survey indicates that, on average, consumers would save 52% in Cincinnati, 58% in Cleveland, 77% in Columbus, and 67% in Toledo by buying the F.D.A.-approved generic equivalent of the

six drugs contained in the survey instead of the brand name drug.

The results of the survey are as follows:

Drug: Brand Name/ F.D.A. Approved Generic Equivalent	Price F.D.A.-Approved Generic Equiv.	Brand Name	Yearly Savings*	% Savings
<u>Cincinnati: Super X Drugs</u>				
Indocin/ Indomethacin	\$16.39	\$36.26	\$290.10	55%
Aldomet/ Methyldopa	\$25.16	\$40.81	\$ 57.05	38%
Diabinese/ Chlorpropamide	\$ 9.99	\$34.35	\$ 88.91	71%
Valium/ Diazepam	\$11.49	\$29.49	\$157.10	61%
Lasix/ Furosemide	\$ 6.29	\$12.34	\$220.83	49%
Inderal/ Propranolol	\$12.49	\$22.01	\$104.24	43%

*/ The annual savings is based on the usual daily dosage specified in the Physician's Desk Reference: indocin/indomethacin - 100 mg; aldomet/methyldopa - 500 mg; diabinese/chlorpropamide - 250 mg; valium/diazepam - 15 mg; lasix/furosemide - 400 mg.; and inderal/propranolol 120 mg.

Drug: Brand Name/ F.D.A. Approved Generic Equivalent	Price F.D.A.-Approved Generic Equiv.	Brand Name	Yearly Savings*	% Savings
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Cleveland: Drug Mart

Indocin/ Indomethacin	\$13.98	\$33.98	\$292.00	59%
Aldomet/ Methyldopa	\$22.98	\$39.95	\$ 61.94	42%
Diabinese/ Chlorpropamide	\$ 6.98	\$33.95	\$ 98.44	79%
Valium/ Diazepam	\$ 7.77	\$26.98	\$210.35	71%
Lasix/ Furosemide	\$ 6.33	\$10.69	\$159.14	41%
Inderal/ Propranolol	\$ 8.99	\$20.37	\$124.61	56%

Cleveland: Revco

Indocin/ Indomethacin	\$10.19	\$32.37	\$323.83	69%
Aldomet/ Methyldopa	\$23.79	\$41.33	\$ 64.02	42%
Diabinese/ Chlorpropamide	\$ 8.99	\$34.62	\$ 93.55	74%
Valium/ Diazepam	\$ 8.99	\$30.22	\$232.47	70%
Lasix/ Furosemide	\$ 6.49	\$10.74	\$155.13	40%
Inderal/ Propranolol	\$ 8.77	\$19.99	\$122.86	56%

Columbus: Drug World

Indocin/ Indomethacin	\$22.24	\$61.04	\$566.48	64%
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Drug: Brand Name/ F.D.A. Approved Generic Equivalent	Price		Yearly Savings*	% Savings
	F.D.A.-Approved Generic Equiv.	Brand Name		
Aldomet/ Methyldopa	\$17.98	\$43.50	\$ 93.15	59%
Diabinese/ Chlorpropamide	\$ 8.99	\$30.69	\$ 79.21	71%
Valium/ Diazepam	\$ 6.99	\$28.44	\$234.88	75%
Lasix/ Furosemide	\$ 3.99	\$10.49	\$237.25	62%
Inderal/ Propranolol	\$ 5.99	\$19.39	\$146.73	69%

Columbus: Revco

Indocin/ Indomethacin	\$ 6.00	\$35.98	\$437.71	83%
Aldomet/ Methyldopa	\$16.90	\$43.01	\$ 95.30	61%
Diabinese/ Chlorpropamide	\$ 4.34	\$38.26	\$123.81	89%
Valium/ Diazepam	\$ 2.84	\$31.94	\$318.65	91%
Lasix/ Furosemide	\$ 4.20	\$11.24	\$256.96	63%
Inderal/ Propranolol	\$ 5.03	\$22.68	\$193.27	78%

Toledo: Bud's Deep Discount

Indocin/ Indomethacin	\$12.30	\$36.24	\$349.52	66%
Aldomet/ Methyldopa	\$24.77	\$41.56	\$ 61.28	40%
Diabinese/ Chlorpropamide	\$ 7.44	\$38.73	\$114.21	81%

Drug: Brand Name/ F.D.A. Approved <u>Generic Equivalent</u>	<u>Price</u> F.D.A.-Approved <u>Generic Equiv.</u>	<u>Brand Name</u>	Yearly <u>Savings*</u>	% <u>Savings</u>
Valium/ Diazepam	\$ 7.91	\$31.78	\$261.38	75%
Lasix/ Furosemide	\$ 4.70	\$14.06	\$341.64	67%
Inderal/ Propranolol	\$ 5.42	\$24.09	\$204.44	78%

Toledo: Lane Drug Company

Indocin/ Indomethacin	\$20.27	\$37.35	\$249.37	46%
Aldomet/ Methyldopa	\$26.80	\$47.66	\$ 76.14	44%
Diabinese/ Chlorpropamide	\$21.21	\$40.02	\$ 68.66	47%
Valium/ Diazepam	\$10.83	\$28.27	\$190.97	62%
Lasix/ Furosemide	\$ 6.75	\$13.37	\$241.63	50%
Inderal/ Propranolol	\$10.20	\$23.06	\$140.82	56%

STATEMENT OF A PANEL CONSISTING OF JERE E. GOYAN, DEAN, SCHOOL OF PHARMACY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, SAN FRANCISCO, CA; AND RINALDO V. DeNUZZO, PROFESSOR, ALBANY COLLEGE OF PHARMACY, UNION UNIVERSITY, AND PHARMACY CONSULTANT, NEW YORK STATE DEPARTMENT OF HEALTH, ALBANY, NY.

Dr. GOYAN. Thank you very much, Senator. I am very pleased to be here today and take part in the discussions in this particular matter.

My name is Jere Goyan and I am Dean of the School of Pharmacy at the University of California in San Francisco. In addition to my 20 years as dean, I served from 1979 to 1981 as Commissioner of Food and Drugs of the U.S. Food and Drug Administration.

I think it is only appropriate that since I have seniority to Dr. Young that I should go before him. [Laughter.]

In both of those positions, I have had a continuing interest in the difficult balancing act the Federal Government engages in, that of attempting to expedite the development and approval of new drugs while trying to contain their cost.

As one who believes that the health of a patient's pocketbook should not be inversely proportional to the benefits he or she acquires through drug therapy, I have long been a strong supporter of the present system which rewards innovator companies with exclusive marketing privileges for a number of years, but which then allows competitors to enter the marketplace after the patent expires.

In response to ordinary market pressures, this has ultimately resulted in significant decreases in the cost of a particular drug therapy, as you noted earlier. I am here today because of my concern that some of the innovator companies have chosen to tamper with ordinary market pressures by sowing misinformation about generic drug products.

I think it would be worthwhile to spend a little time putting this in some historical context. Prior to the 1950s, conventional wisdom was that if two different tablets contained the same drugs in the same quantity, usually referred to as pharmaceutical equivalents, they would have the same effect in the body.

At that time, however, Dr. Eino Nelson undertook research at my institution that would ultimately put an end to this notion forever by demonstrating that various factors could affect the water solubility of a given drug and consequently have a substantial effect on its absorption.

His seminal findings, followed by others, provided us with a basis for understanding the possibility of biological inequivalency between drugs which were deemed to be pharmaceutical equivalents; that is, drugs that were identical in dosage form and strength. The inequivalency can be minor, but it can also be extreme, with two pharmaceutically equivalent tablets not providing the same therapeutic effect.

In November of 1966, I was concerned about the potential for therapeutic failures related to dissolution rate, which is defined as the speed with which a drug dissolves in water, and presented testimony before the Subcommittee on Health, Education and Welfare

of the Assembly Interim Committee on Ways and Means of the State of California.

At that presentation, I enumerated a number of ways in which various physical and chemical parameters might affect dissolution rate. Each was presented with documentation from the literature in which a therapeutic failure had been the result. I, in my written testimony, have gone through a number of these just to explain them. I will not bother with you with that at this time.

But, in conclusion, I noted that serious deficiencies in official standards in manufacturing controls point to the need for a better basis for controlling manufactured products and for assuring their potency.

I further noted that, and I quote, "to build medical care programs of the highest quality is without justification when the advances made are negated by the prescribing of inefficacious products. The patient suffers personally; the community also suffers. The alternative, better control of drug products, is worth the cost to the community and the manufacturer."

In response to concerns similar to those presented by me, one of the first studies of the Office of Technology Assessment of the Congress was devoted to and entitled "Drug Bioinequivalence." Its report, published in 1974, stated as a first conclusion that, "current standards and regulatory practices do not ensure bioequivalence for drug products."

The last recommendation was that, "A system should be organized as rapidly as possible to generate an official list of interchangeable drug products."

Six years later while I was serving as Commissioner of Food and Drugs, the FDA published its first so-called orange book entitled "Approved Prescription Drug Products With Therapeutic Equivalence Evaluations."

In this book, which has been updated every month since its original publication, FDA lists two broad classification categories in which all multisource drugs have been placed: category A, drug products that FDA considers to be therapeutically equivalent to other pharmaceutically-equivalent products, and category B, drug products that FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically-equivalent products. I believe that those products should be phased out, and I believe that FDA is in the process of so doing and I look forward to hearing from Commissioner Young in that regard.

There are a number of subcategories, such as AA, products not representing bioequivalence problems in conventional dosage forms, and AB, and this may be the most important. These are products meeting necessary bioequivalence requirements.

These are examples of products in which it is possible to produce a generically inequivalent product, but for which evidence has been filed with FDA demonstrating bioequivalence with the innovator product.

Bioequivalence is usually based on studies that compare the blood levels elicited by the product of the innovator company with a pharmaceutically equivalent product made by the generic house.

The orange book, therefore, is a clear indication that the agency has responded to the challenge posed by the OTA report and the

concerns of many of us in the health professions. As an outcome, we have a system in place that protects the American people from the potential hazards of bioinequivalence.

As might be expected, generic drugs were not initially warmly received by the prescribers of America. They had some help in this attitude because they were routinely bombarded with advice from the innovators that only brand-name products could be universally relied upon.

But that appeared to die down for a while and it seemed as if everyone, innovators included, had accepted the fact that generic drugs were here to stay. True, some were flawed, and whenever such a report appeared in the literature it was quickly reprinted by the innovators and distributed to physicians and pharmacists.

But for the most part, generic products performed quite well in the patient and the marketplace; so well, in fact, that a large number of brand-name manufacturers began to produce their own generic drugs. This all changed with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984. All of a sudden, new doubts about generic drugs were raised. Once again, generic drugs were under attack.

Frankly, I cannot help but believe that these attacks were primarily motivated by simple economic fears of the potential loss of marketing monopolies for drugs approved after 1962, drugs which account for significant portions of a particular company's income, benzodiazepine, or Valium, and propranolol, or Inderal, for example.

Consequently, the manufacturers of drugs which were going off patent and which were made available by the DPC/PTR have launched a campaign to discredit the generic manufacturers and their ability to manufacture therapeutically equivalent products.

These efforts were not initially targeted to the patient, who generally has little say over the drug product selected, but rather to the health professionals involved, the pharmacist and the physician.

In particular, efforts were made to frighten physicians relative to the possibility of therapeutic failure if they prescribed generic products. Certainly, if one drug is only a third as costly as the innovator product but does not work, it is no bargain.

However, despite all the rhetoric and theoretical constructs for such a catastrophe, they simply have not occurred. Although reports have circulated among professionals, sometimes in the literature and sometimes by word of mouth, that generic drug "x" was causing problems at institution "y," whenever FDA has investigated the allegations, they have uniformly been unable to document inequivalence problems.

Indeed, because of the continuing concerns being expressed, the FDA decided to let the pharmaceutical industry air its case in the fall of 1986. This conference was seen by many as a golden opportunity for the innovator companies to present in a public forum of their scientific peers the evidence for bioinequivalence.

It has been reported that the Pharmaceutical Manufacturers Association conceded that although scientific evidence was not available, they felt that there were cases of such inequivalence—a sorry

anecdotal kind of position if it is true for an industry that thrives on the scientific method.

Dr. Robert Temple of the FDA commented at that time that if PMA's desperate search for such evidence of therapeutic inequivalence had not borne fruit, one might conclude that it does not exist.

At the end of the three-day hearing, Commissioner Young noted that as a scientist he was shocked by the lack of science and clinical data presented to justify the oft-repeated industry allegations and found, I quote, "sophomoric the concept that it is out there; we just cannot find it."

In spite of the lack of data demonstrating therapeutic failures, the industry has continued to harp on the possibility of such failures, raising the specter time after time of problems which occurred in the past, such as those I alluded to in my presentation in California in 1966.

Why have they done this? The answer is simple. It is a way of trying to protect their market share. They obviously have been successful in doing so to a large extent and have even gone so far as to guarantee their income by increasing the unit price of their imitated drug when the generic equivalent drug has come on the market.

Senator METZENBAUM. Dr. Goyan, do you think that you could take a couple minutes more and wind up?

Dr. GOYAN. Fine; that will do very well.

I was going to mention a couple other examples, the one that you did not mention in your opening remarks, the one reported with regard to Ayerst, who believed not only in the stick approach that they used in California with pharmacists, but a carrot approach that they proposed with physicians when they established, I would call it, a frequent flyer program for physicians.

In that program, Ayerst awards points to physicians for each patient for whom the physician prescribes their product, Inderal L.A. Physicians who prescribe this product for 50 patients and fill out a marketing survey earn a free airline ticket to any place in the United States.

The same company has sponsored a comparative study of drug prices which supposedly showed that an important number of consumers paid more for generics than for brand-name drugs.

In a letter to the editor of JAMA, I pointed out that the study failed to make mention of something hidden within its own data, specifically that the average savings for generic drugs covered by the study was \$7.50 per prescription.

But Ayerst is not alone. A number of other companies have been guilty of similar types of activities; Pfizer, for example, the one that you mentioned, and also Sandoz. The companies involved come up with all sorts of innovative approaches to winning friends and influencing people.

For example, it is becoming relatively common for companies to offer a "clinical trial" of an already marketed drug in which physicians and pharmacists are offered a sum of money for each patient enrolled in the trial.

The health professional is then expected to complete a brief report which is filed with the company's medical department. Oftentimes, the drug is relatively new and is being considered for in-

clusion on the hospital formulary, making the true reason for such support of uncontrolled and basically unusable data quite clear.

A magazine called Medical Advertising News had an editorial a few months ago which I thought put it very well. They pointed out for the record the fact that many of the major companies are actually in the generic business themselves while at the same time disparaging the FDA's ANDA process for the approval of generic drugs saying the process does not work.

The editorial ended up by saying, "The problem is that when companies go to great lengths to educate, inform and promote the inequalities of the abbreviated approval system specifically with regard to bioequivalents, how can they turn around and use that same system to seek product approvals? They lose their credibility; the industry loses its credibility." That is from Medical Advertising News.

There is little I can add to that well-stated editorial piece. In my estimation, these research-intensive pharmaceutical companies are indulging in marketing practices which are highly inappropriate for members of the health industry.

Thank you very much.

[Statement follows:]

My name is Jere E. Goyan and I am dean of the School of Pharmacy at the University of California, San Francisco. In addition to my 20 years as dean, I served from 1979 to 1981 as Commissioner of Food and Drugs of the U.S. Food and Drug Administration. In both of these positions, I have had a continuing interest in the difficult balancing act the federal government engages in, that of attempting to expedite the development and approval of new drugs while trying to contain their cost.

As one who believes that the health of a patient's pocketbook should not be inversely proportional to the benefits he or she acquires through drug therapy, I have long been a strong supporter of the present system which rewards innovator companies with exclusive marketing privileges for a number of years, but which then allows competitors to enter the marketplace after the patent expires. In response to ordinary market pressures, this has ultimately resulted in significant decreases in the cost of a particular drug therapy. I am here today because of my concern that some of the innovators have chosen to tamper with ordinary market pressures by sowing misinformation about generic drug products.

Let me start by putting this debate in some historical context. Prior to the 1950s, conventional wisdom was that if two different tablets contained the same drug in the same quantity—so-called pharmaceutical equivalents—they would have the same effect in the body. At that time, however, Dr. Eino Nelson undertook research at my institution that would ultimately put an end to this notion forever by demonstrating that various factors could affect the water solubility of a given drug and consequently have a substantial effect on its absorption. His seminal findings, followed by others, provided us with the basis for understanding the possibility of biological inequivalency between drugs which were deemed to be pharmaceutical equivalents, i.e. drugs which were identical in dosage form and strength. The inequivalency can be minor, but it can also be extreme with two pharmaceutically equivalent tablets not providing the same therapeutic effect.

In November of 1966, I was concerned about the potential for therapeutic failures related to dissolution rate (defined as the speed with which a drug dissolves in water) and presented testimony before the Subcommittee on Health, Education and Welfare of the Assembly Interim Committee on Ways and Means of the State of California and Means of the State of California. In that presentation, I enumerated a number of ways in which various physical and chemical parameters might affect dissolution rate. Each was presented with documentation from the literature in which a therapeutic failure had been the result. These included:

1. The effect of size of drug particles on dissolution rate.
2. The effect of salt form of the drug on dissolution rate. (Some drugs are available in various salt forms, e.g. the hydrochloride salt, the maleate salt, etc.)

Testimony of Jere E. Goyan, Dean, School of Pharmacy, University of California, San Francisco to the Subcommittee on Antitrust, Monopolies and Business Rights of the Committee on Judiciary of the United States Senate, October 21, 1987.

3. The effect of polymorphism on dissolution rate. (Polymorphism is the ability of a chemical to take on various crystalline forms.)

I also discussed a number of ways in which variations in specialized manufacturing procedures could result in therapeutic failures, including the effect of tablet coatings, tablet compression procedures and the effects of so called inert substances that are commonly included in tablet formulations (e.g. disintegrating agents, lubricants, etc.). In conclusion, I noted that "serious deficiencies in official standards in manufacturing controls point to the need for a better basis for controlling manufactured products and for assuring their potency." I further noted that "to build medical care programs of the highest quality is without justification when the advances made are negated by the prescribing of inefficacious products. The patient suffers personally, the community also suffers. The alternative, better control of drug products, is worth the cost to the community and the manufacturer."

In response to concerns similar to those presented by me, one of the first studies of the Office of Technology Assessment was devoted to and entitled "Drug Bioequivalence. Its report, published in 1974, stated as a first conclusion that "current standards and regulatory practices do not insure bioequivalence for drug products." The last recommendation was that "a system should be organized as rapidly as possible to generate an official list of interchangeable drug products. In the development of the list, distinction should be made between two classes of drugs in drugs products:

1. Those for which evidence of bioequivalence is not considered essential and it could be added to the list as soon as standards of pharmaceutical equivalence have been established and satisfied.
2. Those for which evidence of bioequivalence is critical. Such products should be listed only after they have been shown to be bioequivalent or have satisfied standards of pharmaceutical equivalence that have been shown to insure bioequivalence."

Six years later while I was serving as Commissioner of Food and Drugs, the FDA published its first "orange book" entitled "Approved Prescription Drug Products With Therapeutic Equivalence Evaluations." In this book--which has been updated every month since its original publication--FDA lists two broad classification categories in which all multi-source drugs have been placed:

Category A: Drug products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products.

Category B: Drug products that FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products.

There are a number of subcategories, such as AA (products not presenting bioequivalence problems in conventional dosage forms) and AB (products meeting necessary bioequivalence requirement). The latter are examples of products in which it is possible to produce a generically inequivalent product but for which evidence has been filed with FDA demonstrating bioequivalence with the innovator product. Bioequivalence is usually based on studies that compare the blood levels elicited by the product of the innovator company with the pharmaceutically equivalent product made by the generic house. The "orange book," therefore, is a clear indication that the agency has responded to the challenge posed by the OTA report and the concerns of many of us in the health professions. As an outcome, we have a system in place that protects the American people from the potential hazards of bioinequivalence.

As might be expected, generic drugs were not initially warmly received by the prescribers of America. They had some help in this attitude because they were routinely bombarded with advice from the innovators that only brand-name products could be universally relied upon. But that appeared to die down and for a while, it seemed as if everyone—innovators included—had accepted the fact that generic drugs were here to stay. True, some were flawed and whenever such a report appeared in the literature it was quickly reprinted by the innovators and distributed to physicians and pharmacists. But for the most part generic products performed rather well in the patient and the marketplace, so well in fact that a large number of brand name manufacturers began to produce their own generic drugs. This all changed with the passage of the Drug Price Competition and Patent Term Restoration Act of 1984. All of a sudden, new doubts about generic drugs were raised. Once again, generic drugs were under attack.

Frankly, I cannot help but believe that these attacks were primarily motivated by simple economic fears of the potential loss of marketing monopolies for drugs approved after 1962, drugs which account for significant portions of a particular company's income, benzodiazepine (Valium) and propranolol (Inderal), for example. Consequently, the manufacturers of drugs which were off or going off patent and which were made available by the DPC/PTR have launched a campaign to discredit the generic manufacturers and their ability to manufacture therapeutically equivalent products. These efforts were not initially targeted to the patient who generally has little say over the drug product selected, but rather to the health professionals involved, the pharmacist and the physician. In particular, efforts were made to frighten physicians relative to the possibility of therapeutic failure if they prescribed generic products. Certainly, if one drug is only a third as costly as the innovator product but doesn't work, it is no bargain. However, despite all the rhetoric and theoretical constructs for such a catastrophe, they simply have not occurred. Although reports have circulated among professionals—sometimes in the literature and sometimes by word of mouth that generic Drug X was causing problems at Institution Y, whenever FDA has investigated the allegations, they uniformly have not been able to document inequivalence problems.

Indeed, because of the continuing concerns being expressed, the FDA decided to let the pharmaceutical industry air its case in the fall of 1986. This conference was seen by many as a golden opportunity for the innovator companies to present in a public forum of their scientific peers the evidence for bioinequivalence. It has been reported that the Pharmaceutical Manufacturers Association conceded that although scientific evidence was not available, they felt that there were cases of such inequivalence, a sorry, anecdotal kind of position—if it is true—for an industry that thrives on the scientific method. Dr. Robert Temple of the FDA commented at that time that if PMA's "desperate search for such evidence of therapeutic inequivalence had not borne fruit, one might conclude that it does not exist." At the end of the three-day hearing, Commissioner Young noted that as a scientist, he was shocked by the lack of science and clinical data presented to justify the oft-repeated industry allegations and found "sophomoric the concept that it's out there, we just can't find it!"

In spite of the lack of data demonstrating therapeutic failures, the industry has continued to harp on the possibility of such failures, raising the specter time after time of problems which occurred in the past such as those I alluded to in my presentation in California in 1966. Why have they done this? The answer is simple. It is a way of trying to protect their market share. They obviously have been successful in doing so to a large extent and have even gone so far as to guarantee their income by increasing the unit price of their imitated drug when the generic equivalent drug has come on the market! This, of course, runs counter to all economic theory which predicts that competition will lead to a decrease in prices. But that is in a truly open marketplace. Clearly, pharmaceuticals are not in such an open marketplace and innovator companies have played their role quite cleverly. For example, a number of pharmacists have reported that manufacturers have promulgated the idea that pharmacists would be liable for enormous economic consequences were they to use anything other than the "traditional trademark product." This is seen as misleading and unfair by most pharmacists, but unfortunately, some have bought that argument. Such an approach was used in California by Ayerst Laboratories when it attempted to convince pharmacists that substituting their product (Inderal) with generic propranolol could lead to malpractice suits against the pharmacist. On the other hand, apparently being firm believers in the carrot-and-stick approach, it was reported in the *New England Journal of Medicine* that the same company, Ayerst, has established a "frequent flyer" program for physicians! In that program, Ayerst awards "points" to physicians for each patient for whom the physician prescribes their product, Inderal L.A. Physicians who prescribe this product for 50 patients and fill out a "marketing survey" earn a free airline ticket to any place in the United States."

The same company also sponsored a comparative study of drug prices which supposedly showed that "an important number of consumers" paid more for generics than for brand-name drugs. In a letter to the editor of the *Journal of the American Medical Association*, I pointed out that the study failed to make mention of something hidden within its own data, specifically that the average savings for the generic drugs covered by the study was \$7.50 per prescription. Nevertheless, the

conclusion that one could be charged more for the generic drug was widely advertised throughout the professional community.

Ayerst is not alone. A number of other companies, including Sandoz and Pfizer, have been challenged by FDA relative to their claims of generic inequivalence for some of their products.

There is, of course, no way that the generic manufacturers can compete with the innovator companies in regard to their access to physicians. FDA sources have estimated that the total promotional spending by major drug companies exceeds \$4 billion a year, or almost \$9000 per physician. That sort of spending insures that detail persons and other representing the major industry, will have an attentive ear when they present their case to physicians. In addition, the major companies also spend considerable amounts of money on pharmacists and others who play some role in the choice of drug product. Indeed this is especially the case, in hospitals where the pharmacist plays a larger and larger role in the choice of drugs approved in hospital formularies.

The companies involved oftentimes come up with innovative approaches to "winning friends and influencing people." For example, it is becoming relatively common for companies to offer a "clinical trial" of an already marketed drug in which physicians and pharmacists are offered a sum of money for each patient enrolled in the "trial." The health professional is then expected to complete a brief report which is filed with the company's medical department. Oftentimes, the drug is relatively new and is being considered for inclusion on the Hospital Formulary, making the true reason for such support of uncontrolled and basically unusable data quite clear.

Although many questions have been raised about such behavior, the practices continue at this time.

Last year, Medical Advertising News editorialized relative to the whole issue of generic disparagement. I would like to read you from that editorial which I consider to be remarkably perceptive:

"While not altogether unexpected, recent actions by some research-intensive companies are sure to raise more than a few eyebrows at FDA, the media and consumer groups.

"We're referring to the recent practice of running ads and conducting other forms of promotion, such as PR, that question the standards used by FDA in approving generic drug applications. These techniques suggest that FDA's standards are not strict enough, allowing generic drugs on the market that are not the same as brand-name products. Meanwhile, among the companies that are giving FDA a hard time, namely Ayerst, Ciba-Geigy, McNeil, Roche, Sandoz and Searle, are a couple that are using the abbreviated new drug application mechanism reserved for generics to get new products or lines extensions approved faster...The record shows that since the new ANDA

mechanism has gone into effect, many well-known brand-name companies have filed abbreviated applications to bring out products. Among them are Wyeth, Lilly, Lederle, Abbott, SK&F, and Mead Johnson. The problem is that when companies go to great lengths to educate, inform and promote the inequalities of the abbreviated approval system, specifically with regard to bioequivalence, how can they turn around and use that same system to seek product approvals? They lose their credibility...the industry loses its credibility."

There is little that I can add to this well-stated editorial piece. In my estimation, these "research-intensive" pharmaceutical companies are indulging in marketing practices which are highly inappropriate for members of the health-industry.

To paraphrase my earlier comment, I believe that the status of the patient's pocketbook is far more important than the status of the pharmaceutical industry's pocketbook.

Senator METZENBAUM. Dr. Goyan, when a pharmaceutical company offers an inducement to a physician to use their particular product, does that not go to the integrity of the physician's professional position?

Dr. GOYAN. I certainly believe it does.

Senator METZENBAUM. Pardon?

Dr. GOYAN. I do; I believe it does, yes. In fact, it has been raised by a number of physicians who have been very outraged about this. There have been letters to the New England Journal and others where people have pointed that out.

Senator METZENBAUM. I was with a doctor friend of mine just a couple of days ago who told me that—I do not think the trip was anywhere in the United States he was offered. I think it was an overseas trip, and he looked at the detail man from the pharmaceutical company and said you must be kidding, and he said, no, he was not kidding, and he just escorted him out of the office.

But it seems to me that that so much violates the integrity of the process that it——

Dr. GOYAN. Well, I think it could well boomerang and hurt the company itself with physicians.

Senator METZENBAUM. Besides what has already been discussed, do you know of any attempt by a brand-name drug company to disparage the safety or efficacy of a generic drug that the FDA has approved as being bioequivalent?

Dr. GOYAN. Well, I think over the years there have been many cases of this nature. They are seldom, however, done publicly. They are quite often done by the drug salesman coming into the pharmacy or in to see the physician and making these statements, but not in a place that would be public in any sense.

Senator METZENBAUM. Doctor, I am very disturbed by reports that some journals serving the medical profession are heavily financed by companies which sell drugs or other medical products. I also understand that these journals allow the companies to review articles, edit them, or even veto their inclusion in the publication.

Can the American public rest assured that our health professionals are receiving up-to-date and adequate information if these companies are able to veto or edit articles published in these journals, and have you heard similar reports to that which I mentioned in my question?

Dr. GOYAN. It certainly does occur. It has occurred to me personally. I had an article which I prepared with regard to the use of antibiotics totally emasculated by an editor for a small journal of that nature.

I called the editor and asked why was this done and she said "because we were afraid it would insult or anger some of our advertisers who, after all, are responsible for our magazine being available," consequently I know it occurs. It has occurred to members of my faculty as well, and I think it is scandalous.

We try very hard to tell our students, and I know many medical schools do likewise, not to pay much attention to these journals, which are not truly journals; they are magazines with what appears to be editorial content.

Senator METZENBAUM. What can be done to increase the independence of these journals and the articles they contain?

Dr. GOYAN. I do not think there is much that can be done about that because if there were not pharmaceutical manufacturers paying for those advertisements, there would be no need for such journals.

There are lots of very good journals, like the New England Journal of Medicine and JAMA and others which do take advertising but are not dictated to by the advertisers.

Senator METZENBAUM. I understand that more than half of the FDA-approved generic-equivalent drugs are made or sold by brand-name companies. If so many FDA-approved generic equivalents are made or marketed by the brand-name companies, why is there such a substantial difference in price between the brand-name drugs and the FDA-approved generic equivalents?

Dr. GOYAN. Well, the innovator company tries to maintain the high price for their original drug while at the same time they may be trying to produce a generic drug to compete with another manufacturer and they will have to price that lower, while at the same time trying to maintain the higher price for their own drug.

What they have with their original drug is name identification. The physician remembers their name and uses that name alone.

Senator METZENBAUM. Well, some brand-name drug companies claim that the widespread use of FDA-approved drug equivalents would lead to a drop in pharmaceutical research and development. Do you agree with that?

Dr. GOYAN. I totally disagree with that. The argument has been used for the past 30 years. I have not seen any decrease in efforts by the manufacturers, and indeed that is where they really make the money. The big money is in doing the innovative, new things and coming up with a blockbuster new drug.

I always remember while I was Commissioner that Fortune Magazine carried an article called "Tagamania in the Pharmaceutical Industry," which was related to Tagamet, the drug used for ulcers prepared by Smith, Kline and French, an excellent drug, and it has made a bundle of money for them, quite appropriately, in my estimation.

Therefore, I do not believe they are going to stop doing research. That is where they can make big money.

Senator METZENBAUM. A recent edition of the Journal of the American Medical Association reported on a possible product failure in the Cleveland Clinic by an FDA-approved generic-equivalent drug for epilepsy.

I understand that the case is rather complex and that the FDA is in the process of investigating exactly what happened. Therefore, I will not ask you to comment on whether or not there was a product failure in that case.

However, could you explain some of the possible explanations for the reported observation in Cleveland?

Dr. GOYAN. Certainly. As it happened, I reviewed that particular manuscript when it was submitted to JAMA and I recommended that it be published because I thought it was an interesting observation.

I did not agree with a lot of the rhetoric where they seemed to be willing to extrapolate from one case to the universe, but there are

possible ways in which one failure could happen. For example, it may have been prepared wrong; there is no doubt of that.

It also may be that it was treated wrong; that is, it may have been placed in a place where it got extraordinarily hot and the tablet got dried out, let us say, in some fashion and made so hard that it would not disintegrate and eventually dissolve, and therefore you did not get the same amount of drug into the body. That sort of thing does happen. It happens with generic products; it also happens with innovator products.

Senator METZENBAUM. Senator Thurmond.

Senator THURMOND. Mr. Chairman, I ask unanimous consent that my statement appear in the record following your opening statement.

Senator METZENBAUM. Without objection, so ordered. Also, Senator Hatch has a statement for the record.

[Statements referred to above follow:]

STATEMENT BY SENATOR STROM THURMOND (R-S.C.) BEFORE THE SUBCOMMITTEE ON ANTITRUST, MONOPOLIES AND BUSINESS RIGHTS, SENATE JUDICIARY COMMITTEE, REFERENCE THE COMPETITIVE PROBLEM IN THE PHARMACEUTICAL DRUG INDUSTRY, 226 DIRKSEN SENATE OFFICE BUILDING, WEDNESDAY, OCTOBER 21, 9:30 A.M.

MR. CHAIRMAN:

THE HEARING TODAY WILL FOCUS ON THE GENERIC DRUG INDUSTRY AND ITS CONCERNS WITH RESPECT TO COMPETITION FROM THE BRAND NAME MANUFACTURERS.

AS MY DISTINGUISHED COLLEAGUES ARE WELL AWARE, IN 1984 WE ENACTED THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984, THE WAXMAN-HATCH AMENDMENTS. THIS ACT REVISED THE PROCEDURES FOR NEW DRUG APPLICATIONS AND AUTHORIZED AN ABBREVIATED FDA APPROVAL PROCEDURE FOR GENERIC VERSIONS OF "PIONEER" DRUGS APPROVED AFTER 1962. BECAUSE OF THESE NEW PROCEDURES, THE NUMBER OF GENERICS APPROVED BY THE FDA ON AN ANNUAL BASIS HAS INCREASED BY ALMOST 100%. ACCORDING TO APRIL, 1987 TESTIMONY FROM MR. JOHN NORRIS, DEPUTY COMMISSIONER OF THE FDA, PRIOR TO ENACTMENT OF THE 1984 ACT, THE FDA APPROVED APPROXIMATELY 350 GENERIC DRUGS ANNUALLY. IN THE 12 MONTHS PRECEDING HIS TESTIMONY, THAT NUMBER WAS 673, OR AN INCREASE OF ALMOST 100%.

THE REASON FOR MY REFERRING TO THESE STATISTICS IS NOT ONLY TO POINT OUT THAT OUR 1984 LEGISLATION HAS BEEN SUCCESSFUL, BUT ALSO TO NOTE THAT, GIVEN THE EXTENT OF INCREASE, IT WOULD NOT BE UNUSUAL TO SEE AN INCREASE IN THE NUMBER OF COMPLAINTS FROM GENERIC MANUFACTURERS CONCERNING COMPETITIVE PROBLEMS WITH THE BRAND NAME MANUFACTURERS. I DO NOT MEAN TO, NOR WOULD I, CONDONE

ANY ACTIVITY ON THE PART OF THE BRAND NAME MANUFACTURERS THAT SEEKS TO EMPLOY SCARE TACTICS OR OTHER UNFAIR AND ANTI-COMPETITIVE ACTIVITY IN ORDER TO TAKE MARKET SHARE AWAY FROM THE GENERIC INDUSTRY. THE AVAILABILITY OF GENERIC DRUGS IS CRUCIAL TO CERTAIN INDIVIDUALS IN OUR SOCIETY, AND WE SHOULD DO ALL IN OUR POWER TO INSURE THE QUICK, SAFE, AND COMPLETE AVAILABILITY OF THESE DRUGS.

MR. CHAIRMAN, I WILL BE PARTICULARLY INTERESTED IN HEARING FROM THE FDA ABOUT THOSE ACTIVITIES OVER WHICH THEY HAVE REGULATORY AUTHORITY AND THOSE THAT ARE OUTSIDE THEIR JURISDICTION. I AM ALSO INTERESTED IN HEARING ABOUT THE BRAND NAME MANUFACTURERS THAT HAVE GENERIC SUBSIDIARIES OR DIVISIONS, AND THEIR REACTIONS TO ANTI-GENERIC ACTIVITY.

I THANK THE WITNESSES FOR APPEARING HERE TODAY, AND I LOOK FORWARD TO THEIR TESTIMONY.

STATEMENT OF SENATOR ORRIN G. HATCH

Mr. Chairman, I want to thank you for holding a hearing on this important issue of equivalency between brand name and generic pharmaceuticals. In my tenure as U.S. Senator and specifically in my role as chairman and now ranking minority member of the Labor and Human Resources Committee, I have a great interest in the role of the pharmaceutical industry and their movement to improve people's health. In addition to this effort, in recent years both the industry and Congress are examining mechanisms for controlling health care costs. Because of the need to balance safety and cost issues, I authored the Drug Price Competition and Patent Term Restoration Act which opened the doors for generic copies of the patient medications. This law brought together long sought—and long elusive public policy goals. Both sides of the pharmaceutical industry came together to solve vexing problems in drug development, and formed a union for the American people. They worked on a dual benefit of less expensive drugs today, and the promise of better drugs tomorrow.

Recently, concerns have surfaced regarding the therapeutic equivalency of generic drugs to pioneer products and the competitive implications that such concerns have raised. There is tremendous disagreement about the validity of these claims and I look forward to hearing the testimony of the witnesses on this important issue. Let me also join in welcoming you all here this morning.

Senator THURMOND. I just want to ask you this question. What do you have to offer or recommend for the good of the public in these matters?

Dr. GOYAN. Senator, I have thought a lot about that and it worries me. I feel very strongly about the importance of the patent system and keeping the innovator companies interested in research, and I would not want to do anything to stop that.

So I think if legislation is going to be offered, it is going to have to be very carefully crafted in order to maintain the balancing act I spoke of in the beginning of my testimony; that is, where we are trying to keep the innovator companies innovating, but at the end of their patent monopoly then we have got to get the prices down to a more reasonable range. As I say, I would leave that to the legislators to tell me how to do it.

Senator THURMOND. We certainly want the public to get the benefit of the savings. According to these figures that Senator Metzbaum has acquired here from his home State, there seems to be a big difference in cost. Did you see these figures?

Dr. GOYAN. Yes, I did. They are right there.

Senator THURMOND. On the other hand, if a pharmaceutical company spends millions and millions of dollars to come up with something worthwhile to help humanity and help the public, we do not want to do anything to stymie that, do we?

Dr. GOYAN. I agree.

Senator THURMOND. And so that is a question there that you have got to have a balance to follow a course that is sound that will keep the price of drugs at a reasonable price, and yet encourage the pharmaceutical companies to go forward, do research, and come out with drugs that will be of great benefit to humanity.

Dr. GOYAN. I totally agree. I believe that the companies have a right to set their prices when they first bring the drug on the market at a rate that will repay their costs, not just for that drug but for the dry holes, as they call them, from which they do not get a new drug.

But at the end of that time, I do not think they have the right to start frequent-flyer programs and other things to try and keep

people using their drug when there is an equivalent one available at a fraction of the price.

Senator THURMOND. Thank you very much. Thank you, Mr. Chairman.

Senator METZENBAUM. I would point out to my colleague that in 1984 we had a big battle with respect to patent extension, as well as the question of generics, and a compromise was arrived at.

In retrospect, I am not sure it was the greatest compromise from the standpoint of the public, but we gave the drug companies a 5-year extension on their patents, and in consideration for that they withdrew their objections to the generics being tested and approved by the Food and Drug Administration.

So I think it is fair to say that we recognize that you cannot get drug companies to come up with new products unless they are in a position to make a profit, but we give them 22 years protection under the law. Originally, it was 17 years.

Senator DeConcini.

Senator DECONCINI. Mr. Chairman, thank you.

Dr. Goyan, your testimony is of great interest. I am curious as to where you see, if you do, the activities of the name-brand companies reaching the level of antitrust violations.

Although I am aware that there is an appeal pending in the case against American Home Products, the district court in granting the defendant's motion to dismiss stated, and I quote, "While misleading advertising, including breach of contract and the like, is not competition on the merits, it is likewise not an antitrust violation."

I am not saying that I condone any of those practices of the defendants in the case, but the court clearly found that there was no monopolistic conduct in violation of Section 2 of the Sherman Anti-trust Act.

Do you look at this at all from the antitrust perspective?

Dr. GOYAN. Senator, while I was Commissioner I vowed I would never try and play lawyer, and I really do not know the answer to that. I just know that what is going on I consider to be bad and if it can not be addressed by this subcommittee, it should be addressed by some other subcommittee of the Congress.

Senator DECONCINI. OK, and you have not bothered to seek or did not seek at the time legal advice as to when the antitrust laws ought to apply to this type of a situation where you have competing interests?

Dr. GOYAN. No, sir.

Senator DECONCINI. Now, the PMA testimony discusses several instances where generic drugs caused medical problems for the patient using them. They have also included an appendix with several case summaries of such problems.

Have you had a chance to review that?

Dr. GOYAN. I have not.

Senator DECONCINI. Would you mind taking a look at their testimony and give us your opinion as to the validity of these cases?

Dr. GOYAN. I think that would be literally impossible. You know, just looking at them quickly at this time would not give me an answer with regard to it. I stand by what I said earlier, and that is

that every time the FDA has looked into some of these anecdotal situations, it has turned out not to be verifiable.

Now, these may be, I am not saying they are not. I just do not know and do not know how I could do it.

Senator DECONCINI. Well, just out of curiosity, if you would be so kind as to look at their appendix, not right now—I do not mean now—and if you feel like responding later for the committee, I would appreciate it. I do not know how to assess it.

Dr. GOYAN. I would be happy to do that.

Senator DECONCINI. I was just thinking that perhaps someone with your experience could just give us an opinion of what you think the validity is. Thank you, Dr. Goyan.

Thank you, Mr. Chairman.

Senator METZENBAUM. Thank you, Senator DeConcini. I might say to you that we will return to the matter that you raised concerning the PMA listing of particular situations and Dr. Frank Young will be prepared to speak to that subject as well.

Senator DECONCINI. OK, thank you.

Senator METZENBAUM. Senator Specter.

Senator SPECTER. Dr. Goyan, are there any significant differences between the so-called generic drugs and the patented drugs?

Dr. GOYAN. No, sir, there are not. Once they have been approved by the FDA, they are equivalent.

Senator SPECTER. There have been some specific cases brought to my attention which suggest that there have been different reactions by patients when they take a substitute generic drug.

Do you consider those situations either erroneous, false, or so unusual as not to have any general applicability?

Dr. GOYAN. Well, I think that in the past there were such concerns. In fact, I voiced them myself back in 1966. I think today we have a system in place that makes those extraordinarily rare, and therefore, as you put it, not of great concern.

Now, some have argued that if a patient is very tightly controlled—that is, the amount of drug that they have to have is very, very tightly controlled within very small differences of concentration—that it would be best to stay with one drug for the whole time; that is, if you titrate the patient on drug “x,” then you should not change to another.

Perhaps you titrate them on the original generic drug then you should not go back to the innovator drug; you should stay with the generic drug. I personally do not think that is necessary, but I do know there are people of goodwill who believe that is true.

Senator SPECTER. You say that you had expressed some concerns yourself back in 1966?

Dr. GOYAN. That is right, before the FDA took the—

Senator SPECTER. Excuse me. What concerns had you expressed in 1966?

Dr. GOYAN. The same concerns that are being expressed today by those who raise questions about generic equivalency.

Senator SPECTER. Well, precisely what are those concerns that you expressed in 1966?

Dr. GOYAN. The possibility that the drugs would not dissolve as rapidly and therefore be available in the bloodstream at the same levels as the innovator drug. That may come about because you use

a wrong polymorph for the drug or the wrong salts, something of that nature.

Senator SPECTER. Well, do you think that that issue has been totally resolved at the present time?

Dr. GOYAN. It has to my satisfaction, yes.

Senator SPECTER. But you say that there are others of goodwill, knowledgeable people who have disagreement on that point?

Dr. GOYAN. I do not think that people disagree with me at that level. What they disagree with is they say, well, if you have a drug that is really sensitive in terms of the concentration level in the blood that has to be maintained in a very tiny level of difference, you might be better off to stay with one.

Rather than going from manufacturer "x," "y" to "z" and back, you probably ought to stay with one, and it does not have to be the innovator drug; it may be a generic drug. It is just that between the various dosage forms, it might vary slightly.

However, the reason I do not buy that argument is that you also see the same sort of problems if you look batch to batch with any company. What you produce this month will be slightly different from what you produce next month.

Senator SPECTER. One critical question in my mind is this factual issue as to whether there is a sufficient difference in the drugs so that there is a difference in the brand name as opposed to the generic name.

Would you expand just a little bit more on what you mean by tightly controlled? You say that in situations where a person is "quite controlled," there may be some justification to stay with, if not a generic drug or a brand drug, at least the same drug?

Dr. GOYAN. Yes. Well, again, it is a matter that in certain disease states where you are trying to maintain the drug level at a given point and you do not want it to vary very much from that particular point, you probably have a better chance of getting it time after time if you get it from the same company.

Senator SPECTER. What percentage of people fall into that category of being tightly controlled?

Dr. GOYAN. Oh, I would suspect it is less than five percent, but I do not know.

Senator SPECTER. And how serious are the consequences for that relatively small group of people when they do make the shift?

Dr. GOYAN. I do not know the answer to that exactly. I do not think it is a big problem. Indeed, perhaps the best way of putting it is that when I am able to buy a drug by generic, I buy the generic for myself, for my family.

Senator SPECTER. Dr. Goyan, just one final question. At the conclusion of your testimony, I thought I understood you to say something to the effect that the brand companies do not have the right to use flyers. Did you say something about that?

Dr. GOYAN. No, no. I was talking about the frequent flyer program that Ayerst had come up which said to the physician, if you will write so many prescriptions for our drug, we will give you an airline ticket to go anywhere in the United States.

Senator SPECTER. I see, and you think that is a bad practice?

Dr. GOYAN. Yes, sir, I do, because that forces up the price of those drugs to the patients who have to take them.

Senator METZENBAUM. Does it not also affect their judgment?

Dr. GOYAN. Well, if physicians fall for it. As I said before, I think that a lot of physicians are going to stop using Ayerst products because they are so peeved with the whole idea.

Senator SPECTER. So your point is that that is an unfair inducement which inappropriately seeks to influence physicians' recommendations?

Dr. GOYAN. Well, the pharmaceutical——

Senator SPECTER. I just did not understand what your point was on that.

Dr. GOYAN. Well, the pharmaceutical manufacturers always maintain they are part of the "health care team." If they are going to be part of the health care team, they have to behave in what I consider to be a reasonable manner, and I think paying physicians to prescribe my drug is not a reasonable manner. I think it is a kickback.

Senator SPECTER. How widespread is that practice?

Dr. GOYAN. Well, the one that I mentioned is in place, the Ayerst frequent flyer program. How many others there are, I do not know.

Senator SPECTER. Thank you very much, Dr. Goyan. Thank you, Mr. Chairman.

Senator METZENBAUM. Dr. Goyan, one last question concerning Senator Specter's inquiry. It is a fact, is it not, that the FDA is aware that there are some generics that have some variation as far as dissolution rate and matters such as that, although they may have the same bioequivalency?

In those cases, those are placed on the B list and therefore, as I understand it, are not certified for marketing, is that right?

Dr. GOYAN. That is right. This is what I said but it is wrong, they are certified but identified as pharmaceutical alternatives rather than generic.

Senator METZENBAUM. Thank you very much, Dr. Goyan.

[Response to questions:]

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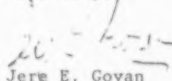
November 12, 1987

Senator Howard M. Metzenbaum
Chairman, Subcommittee on Antitrust,
Monopolies, and Business Rights
Committee on the Judiciary
United States Senate
Washington, DC 20510-6275

Dear Senator Metzenbaum:

Enclosed is my response to the questions submitted to me in your letter of November 2nd. I hope it will be helpful.

Sincerely,


Jerrold E. Goyan
Dean

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Enc.

Questions submitted by Senator Metzenbaum to Dr. Goyan

1. In your testimony you refer to a study sponsored by Ayerst Laboratories that supposedly showed that "an important number of consumers paid more for generics than for name brand drugs." You also indicated that you had criticized that study in a letter to the editor of the Journal of the American Medical Association. Can you briefly describe what problems you saw with the study?
2. In your testimony you were critical of non-medical inducements offered by some pharmaceutical companies to encourage doctors to prescribe their products. One such inducement, the Ayerst "frequent flyer" promotion was discussed at length. In addition to that particular program, what other non-medical inducements are employed by pharmaceutical companies? Please provide as much detail concerning each as is possible.
3. The PMA provided an appendix to its testimony detailing cases where it contends generic drugs were substituted for name brand drugs producing an adverse reaction. While the Subcommittee is not expecting you to undertake any independent investigation, we would appreciate whatever insight you could offer concerning whether you think these cases support the contention that substitution of FDA approved bioequivalent drugs is unwise.
4. One issue raised at the hearing was whether once a patient was titrated to a particular drug, a bioequivalent drug should be substituted. First, could changing from one lot to another lot of the same drug by the same manufacturer present the same problems that could be created by changing from a name brand to a generic bioequivalent? Second, at the hearing you testified that perhaps less than 5% of people fall into the category of being tightly controlled by medication and thus might be advised not to switch from a drug made by one company to a bioequivalent drug made by another company. Generally, where a patient is tightly controlled do physicians make an effort to monitor closely the medication that patient receives? If such a patient wanted to use a generic bioequivalent for financial reasons, could such a change be made safely?

Question 1:

The study funded by Ayerst Laboratories referred to in my testimony was published in the November 14, 1986 issue of the Journal of the American Medical Association. On the surface, it is an impressive venture, involving an audit of nearly 900,000 prescriptions comparing the prices of brand-name products with their generic equivalents in more than 1,300 pharmacies in 39 states. Shortly into the article, the authors make the statement that "that generic drugs "usually cost less," although "an important number of consumers paid more."

The latter portion of that statement is jolting because it attacks all prior notions that generic drugs are consistently cheaper than their brand-name counterparts. It is such a striking indictment that it has been widely quoted in the lay press and exploited by others for marketing purposes. One such was Hoechst-Roussel, a major manufacturer of brand name drugs, which distributed the following press release entitled, "Landmark Study Concludes Generics Are No Guaranteed Bargain:"

"Are consumers saving money when they buy generic drugs rather than name brands? Usually, but not always, reports a recent study....In fact, according to (the) researcher...an 'important' number of consumers pay more for generic drugs than for their brand-name equivalents."

The imposing statement that gave birth to this disseminator of misimpressions is curious from many points of view. First of all, it is ambiguous, something that is avoided like the plague in scientific publications of any merit.. Imagine, if you will, a so called scientific study that provided no figures but claimed that an important number of AIDS patients had been cured by a previously unknown drug. It would not be taken seriously by skilled scientists. Similarly, the authors of this study do not provide any dimension to their "important number." Is it fifty persons, a thousand, ten thousand? And what data leads to this conclusion? If it is buried there somewhere in their figures, the authors fail to point it out.

Taken on the surface, the inevitable impression left by this undocumented statement is that in the ordinary event of having a prescription filled at the pharmacy of their choice, some patients--an "important number" of them--would pay a premium price for generic drugs. If one carefully analyzes the design of the study, however, one realizes that the cost determinations are based upon batched data from different pharmacies. In other words, the generic prescription was filled by one pharmacy and the brand-name counterpart by another pharmacy which may actually have been in another city or another state. That is not the way consumers ordinarily have their generic vs brand-name prescriptions filled.

They do not shop for generics in one pharmacy and branded drugs in another and they definitely do not do shop in this manner by flying across the nation. If they did, they might discover that due to economic factors (the cost of doing business, etc.) a prescription filled with a brand-name product in Helena, Montana, for example, may occasionally be cheaper than a generic product filled in San Francisco. But the fact of the matter is that in their hometown pharmacy, a generic drug will consistently be cheaper than its brand-name equivalent. The authors appear incapable of appreciating this.

Most interesting of all is that the author's chose not to reveal one of the most obvious and striking findings of their study. If one takes out a calculator and works with their data, one finds that the average savings for the generic prescriptions covered in the study was \$7.50 per 100 capsules or tablets. That is a significant savings and suggests to me that the "important number" referred to earlier--if it actually exists--cannot be so important after all. In fact, in the aforementioned Hoechst-Roussel press release the author's admitted that this "important number" saved only "a couple of bucks more" and a couple, in my mind, is considerably less important than \$7.50. It does not require a Ph.D. in economics to reach that conclusion.

In addition, the authors reveal their inability to understand the data they have collected by their statement that there is no guarantee that:

"A pharmacy will not dispense a generic drug and charge a price similar to that of a brand-name drug to improve profit margins."

Nowhere in the data is the aforementioned inclination or motive supported. There is, however, some data regarding "percentage of profit" in which the authors seem to be pointing out that pharmacists receive a higher "profit" from generic drugs than brand name drugs. Herein they reveal their ignorance of how retail prescription drug prices are established.

By and large, prescription prices are calculated on the basis of a set professional fee + the cost of the drug. e.g. if a particular pharmacy's fee is \$5.00 and a particular brand name drug costs the pharmacist \$4.00, the prescription charge would be \$9.00. If, however, one were to take the cost of the drug (\$4.00) and calculates so-called profit based on the ultimate charge, the profit would appear to be 225 percent.

Generic drugs cost the pharmacist less and let us assume that the same drug is available in a generic form and costs the pharmacist \$2.00. The ultimate charge, therefore, would be \$7.00, but the profit (computing it as the authors did) would be 350 percent. In each case, the pharmacist's actual "profit" has been exactly the same (because it is based on the set professional fee). Of note, however, is that even if one buys the notion that pharmacists profit more from generic drugs, the fact of the matter is that they are still significantly cheaper than brand name products.

The authors' careless wording and poor science do considerable damage and mislead even those whom might ordinarily be expected not to be gullible. One such person was Dr. Louis Lasagna who apparently did not analyze the data carefully and was so moved by the authors' smoke screens that he wrote a covering editorial in the same issue of JAMA. One of the things he said was that the study showed that "a brand-name drug from one store is cheaper than a generic version from another (or the same store).

The authors didn't exactly say that but their blurry messages definitely left that open as a possibility. Regardless, Dr. Lasagna's published misimpression is a sterling example of how potentially damaging this particular study has been and undoubtedly delighted those who wish that generic drugs would go away.

Question 2:

The Ayerst "frequent flyer" program is the only one I am aware of in which a prescriber may earn some kind of premium for prescribing a particular product, Inderal LA. There are, of course, other forms of inducements used by manufacturers that are not so direct. Occasionally a physician who is known to routinely prescribe a particular drug will be given an all expense paid "continuing education" junket of some kind to an exotic place, sometimes gifts are proffered to preferred prescribers and occasionally "grants" will be given to particular prescribers to perform a kind of "clinical study" on an existing drug that simply reproduces something that is already known. All of these, of course, might be defended by manufacturers as goodwill gestures and are not a direct payment per prescription as is the case in the "frequent flyer" program. Incidentally, I should note that the product so rewarded is a form of propranolol for which there is no generic equivalent. Thus, the prescription would capture the patient permanently for the Ayerst product.

Question 3:

Not having had access to PMA's appendix, I can only comment on the basis of prior experiences with their efforts to cast doubts on generic drug products. Over the last three or so years, a number of review articles or correspondences have appeared in medicine and pharmacy's professional journals, most of which have been written by representatives of the pharmaceutical industry. On the surface, these are impressive documents which provide lengthy lists of references and cite all of the things that can go wrong in dosage form design and production which might affect the ultimate disposition of the drug in the body. The fact of the matter is that most of the points made are either shopworn--ala phenytoin, digoxin and theophylline--or hypothetical, i.e they have little, if anything, to do with clinical reality. What is discovered in them are the potentials for horror, not in most cases documented evidence of such horrors. If read carelessly, however, one could easily come to the conclusion that generic drugs are junk. As I stated in my

testimony, this just isn't the case. Both experience and science have shown that, overall, generic drugs perform rather well. The relatively few that fail do not represent the entire species and are by no means adequate justification for the statement made by the author of one such article who said that "the risks associated with...substitution appear to outweigh any benefits that may accrue from this practice."

Question 4:

This is a question that is probably best answered by the FDA. Nevertheless, due to the limits of manufacturing processes, there is bound to be variability in the bioavailability of different batches of the same drug, brand-name or generic. Because this is not something that companies monitor for, (they maintain standards by other tests such as dissolution rate, etc.) a patient who is being maintained on a critically titrated drug could possibly come to harm.

Your question regarding whether physicians make an effort to closely monitor drugs that must be tightly titrated can only be answered with a response that some do and some don't. The problem is a highly complex one relating to the fact that some prescribers are aware of the potentials for harm from the medications they prescribe and some, plainly, are not. The former are reasonably up-to-date and order appropriate labs tests for blood levels, etc., or otherwise physically monitor their patients for improvement and/or adverse effects. The others tend to rely upon standard reference sources that suggest so many doses over a given period of time and do not, therefore, realize the damage their prescriptions may inflict. (At particular risk in this regard are the elderly whose bodies do not respond to drugs in the same way as the young.) Fortunately, the matter is steadily improving, especially as increasing numbers of the new breed of pharmacist (the clinical pharmacist) enter practice. These practitioners are highly skilled in the clinical use of drugs and are trained to intervene whenever necessary to assure that patients receive optimum therapy.

The most difficult portion of your question to answer is "If a (patient receiving a tightly monitored drug) wanted to use a generic bioequivalent for financial reasons, could such a change be made safely?" The answer is a qualified "yes". Yes if the drug is actually bioequivalent (an FDA rating of AB) and yes if the physician is one who carefully monitors his or her patients.

Switching between brands for drugs that must be critically titrated, however, is not a good idea primarily because bioequivalency may be less certain when considering switching between different sources than it is between different batches of the product from the same manufacturer. Frankly, we do not have studies to address this problem. However, as you noted at the hearings, there have been more complaints about lack of efficacy with Primidone than with its generic competitors. Such findings might be explained by batch to batch variation, but we do not know.

In certain instances, the problem of monitoring becomes quite complex. For this reason, we generally advise people who are receiving a critically titrated drug to

stay with the same manufacturer for the entire duration of their therapy. However, I would like to re-emphasize my conviction that this represents a tiny percentage of patients and should not be used to damage the reputation of generics, especially since it is only a theoretical risk.

Conclusion

In my opinion it is unfortunate that so much time and money and effort has been devoted to this issue because in the final analysis, the engine that has driven it is not health care but economics. In comparison to the real problems associated with drug therapy--inappropriate prescribing, over-prescribing, drug abuse, drug interactions, drug overuse, non-compliance to list only a few--the few problems caused by inequivalent drugs pales into insignificance.

John E. Goyan

Senator METZENBAUM. Our next witness is Dr. Rinaldo V. DeNuzzo, Professor of Albany College of Pharmacy of Union University, and pharmacy consultant for the New York State Department of Health, Albany, New York.

I tried, Mr. DeNuzzo, to let the matter go a little loose, but I am afraid I will never get to all the witnesses so I am going to limit witnesses to five minutes. We will make an exception for Dr. Young when he appears.

Mr. DENUZZO. Thank you very much, Senator Metzenbaum. It is a pleasure to be here. It is nice to see you, Senator Thurmond.

My name is Rinaldo DeNuzzo. I am not a doctor; I am a pharmacist and an educator from Albany, NY, with an academic appointment as a professor of pharmacy at the Union University College of Pharmacy. I also hold a position as a consultant pharmacist to the New York State Department of Health.

Senator METZENBAUM. Could you speak up just a little bit?

Mr. DENUZZO. Sure. I teach pharmacy law, pharmacy management, and pharmacy marketing. My responsibilities with the Department of Health include an appointment as chair of the Technical Pharmacy Advisory Committee, which is charged with the decision of which products will appear on the medical assistance formulary for use by individuals who qualify for payment. This puts me in contact with representatives of the brand-name drug industry.

I am the author and originator of the annual prescription survey which began in 1956, and I am currently accumulating data for a 32nd report. I do or have done other forms of market research with respect to the delivery of prescription and non-prescription drugs to patients in the ambulatory or out-patient environment and to residents in skilled nursing facilities.

These research activities presented me with an opportunity to assist New York State in the implementation in 1978 of a special two-signature prescription line blank which was designated to increase the use of less expensive therapeutically-equivalent drug products for brand-name items.

Among my many activities at that time was to direct the publication of a paperback titled "Safe, Effective, and Therapeutically Equivalent Prescription Drugs," which was a forerunner of the federal orange book, and also to project potential savings for consumers and to measure success of this particular legislation.

I would like to address prescription drugs hurriedly. They are unique in that they represent a directed consumer good. This means that the user of the product is directed to do so by a prescriber who is the true consumer. We have a situation here where one person makes a purchasing decision for another and, I am of the opinion, often with scant regard for the costs involved and with no personal economic risk.

In addition, I would like to go to the orange book, the universe of FDA-approved prescription drug products, which currently includes some 9,429 drugs, of which 7,306, or 77.5 percent, are available from multiple sources, and 6,309—86.4 of them have therapeutically equivalent products in the marketplace.

With these FDA statistics and information I accumulate annually about the prescription drug market, there is currently more

than 500 million of 800 million new prescriptions dispensed annually for which there are multisource products. I estimate this market to be in excess of \$7 billion, and it is a sizable market to retain, gain, or lose.

Multisource drug products may differ in color, size, shape or flavoring. The major difference, however, is the amount that consumers pay for the product, which is approximately 50 percent less than a therapeutically equivalent brand name drug product.

This is possible because generic drugs are no longer the exclusive property of the original developer or patent-holder and a manufacturer can produce them at a lower cost, thereby passing the savings on to the consumer.

Education has been attempted by the Federal Government and by the State of New York. In fact, I took an active role in our educational process in New York State in an attempt to allay the fears of prescribers who write prescriptions for generic drugs, in that they are going to be liable, and also for patients, in that they are not convinced that they are going to get the drug which will do the job.

In spite of all attempts to educate the public, issues continue to surface which create doubts in the minds of the prescriber and patient alike. One theme appeared in a magazine, a controlled-circulation magazine which is sent to diabetic patients.

In this magazine, the patient was given considerable information about the disease state and then finally the message is if you are using a brand name product, should you really take a chance on a generic, because who knows what is going to happen 15 years down the line? I certainly do not know and I am convinced that patients certainly would not know.

Once again, in spite of this, I continued to have information directed at me from prescribers. I received two letters within the last 8 days from neurologists unknown to me concerning impending legislation on the part of the Health Care Financing Administration which would set specific upper limits of payment for multiple-source and other drugs as of October 29, 1987.

In my position as chair of the Technical Pharmacy Advisory Committee in New York State, I often receive multiple mailings within a short time span. Quite often, the only difference in each letter is the name and address of the sender. I call it an orchestrated response in order for me to consider doing something positive for the brand name drug industry.

There is an article that appears in——

Senator METZENBAUM. Could you take a minute to wind up, please?

Mr. DENUZZO. Sure.

There is an article that appears in the Consumer's Report. There is an article in Forbes magazine that appears on this topic, and I am of the opinion that if the material in these two articles was not truthful, these magazines would be subject to libel suits and would be taken to task in the legal system, and I find that it has not happened.

With that, I will wind up. Thank you very much.

Senator METZENBAUM. Thank you very much, Professor DeNuzzo. One of the marketing tactics that Ayerst Laboratories has

used is to send an expert around the country and make him or her available to the press to discuss the issue of generic drugs.

For example, a letter from a media tour coordinator—that is their term, not mine—of the public relations firm hired to run the tours to a New York television station quotes one of these experts as follows: "With generic substitution, the patient is at risk. He may sometimes receive an inferior medication with no way of being certain that what is dispensed is exactly what the doctor ordered." Do you believe that statement is accurate?

Mr. DENUZZO. No, I do not. I want to give a caveat. If the drug that we are talking about is one which has been determined to be therapeutically equivalent, I would state that it is a patent falsehood.

Senator METZENBAUM. What impact do you think statements like that have on the public?

Mr. DENUZZO. They create fear and doubt in the minds of the consuming public.

Senator METZENBAUM. Here are some news clips: "Generics Controversy Continues," from West Palm Beach; "Doctor: Generic Drug Use Could Result In Problems"; "Generic Drugs May Have Hidden Dangers"; "Caution Urged on Generic Medications," et cetera.

My question is whether or not that is fair to the American consumer to have pharmaceutical manufacturers having people out in the field ostensibly as experts, but really providing a loaded-dice kind of approach to the whole question. Do you have any comment on that?

Mr. DENUZZO. I do not believe it is fair, and it puts individuals like myself in jeopardy when we try to tell the other side of the story because you hear two tales and then you begin to wonder just who in heaven's name is telling the truth.

Senator METZENBAUM. Have the pharmaceutical manufacturers ever attempted to put any pressure on you personally?

Mr. DENUZZO. Individually?

Senator METZENBAUM. Yes.

Mr. DENUZZO. Well, there was a movement in the State of New York within the last session to remove the committee that I serve from the Department of Health to the Department of Social Services. That action was taken, I am told, by the Pharmaceutical Manufacturers Association.

Now, I must be candid with you. I am a pretty independent cuss. I will not allow any drug manufacturer representative even to buy me a cup of coffee because I do not want to be beholden to anyone, at least not at my age in life.

Senator METZENBAUM. Do you think it is all right younger?

Mr. DENUZZO. I think it is all right, yes.

Senator METZENBAUM. One last question: Another tactic some companies have used is to send letters to pharmacists, physicians, or State formulary committees suggesting that generics should not be used.

For example, in February of 1985 Pfizer, Inc., attempted to keep generic competitors of its product Diabinese off the Illinois formulary by writing to formulary committee members that the generic was inferior.

The FDA, in response, told Pfizer that it considered Pfizer's actions "an attempt to falsely malign both the generic drug industry and, more importantly, FDA's system for ensuring therapeutic equivalence in approved generic products."

Have you seen similar letters either in your capacity as a pharmacy professor or as a consultant to the State of New York, and what potential, if any, impact do you think such letters have?

Mr. DENUZZO. Well, on the committee that I chair, they have a very negative effect because these individuals are all valued professionals and they can see right through this every day in the week.

There are other pressures that are brought to bear. If you cannot prevail on the committee, then the legal route will go and quite often a law will be passed to undo what you attempt to do.

As chairman of that committee, I have two letters that I received within the last eight days from neurologists telling me of the dangers associated with the use of generic anti-convulsive drugs.

I have some information. The committee looked at a product marketed by Schering, a New Jersey-based organization. We publish our agenda 72 hours before our meetings. I received information from physicians in New York State, and I also received a letter from an Oregon-based dermatological group giving me the advantages for including the brand name product and, as I read the information given me, I want to say, incomplete information. That is the kind of material that I see as chair of this committee.

Senator METZENBAUM. Do you think that those letters from doctors were pharmaceutical company-stimulated?

Mr. DENUZZO. Well, in the one instance, a copy went to the pharmaceutical government representative, so I presume that before the fact he knew that the letter was coming.

Senator METZENBAUM. A reasonable conclusion. Thank you.

Senator THURMOND.

Senator THURMOND. Thank you very much. I just wanted to ask you this question. From your vast experience as a professor and as consultant to the State of New York, what advice would you give the public in buying drugs?

Mr. DENUZZO. I tell the public to shop for their prescription. I put together a list of 60 approximate cost comparisons which I passed out at the 1987 New York State Fair, and I do occasionally appear on WGY, a 50,000-watt radio station in the capital district, and I give this message in each and every instance: Talk to your doctor, talk to your pharmacist, shop for the best possible drug price.

If you want to pay 75 or 80 cents more for a prescription for service, fine. But, certainly, a knowledgeable consumer should know what the consumer is buying.

Senator THURMOND. From your experience, do you feel that the FDA-approved drugs that have been tested are just as safe and just as effective as the pioneer drugs?

Mr. DENUZZO. Senator, I believe in the Food and Drug Administration. If I believe that the Food and Drug Administration can make a decision on a pioneer drug, then they have the capability to make that same decision on a multisource counterpart.

If I trust the system, and I implicitly do—if I trust the system, then I trust the system. I cannot trust the system 50 percent of the time and not trust the system the other 50 percent of the time.

To repeat, if FDA has the ability to say, yes, here is a brand new product and you can use it in the American public, I am convinced they have the same technology to say here is one that is quite like it; it is also safe.

Senator THURMOND. How often do you publish the publication you held in your hand there a moment ago, and what distribution do you give that?

Mr. DENUZZO. This publication, the price listing—is that the one you are referring to?

Senator THURMOND. Yes, sir.

Mr. DENUZZO. The price listing is available to anyone who wants it. I distributed it, approximately 10,000 of them, at the New York State Fair. It served as a kick-off for introduction of a new prescription drug program in the State of New York effective October 1, called EPIC, and it also served as consumer information.

Senator THURMOND. You distribute that to the drug stores and pharmacies in New York State?

Mr. DENUZZO. Yes, sir, Senator. This information is available to anyone who wants it, and in the State of New York we require that a price poster appear so that the public will know what the public is going to pay for a particular prescription in a given quantity and a given strength and, in addition, there is a comparable price for the generic product.

Senator THURMOND. Now, does the law require that to be published somewhere where the public can see it?

Mr. DENUZZO. The prescription price list has to be—I like to use the word “juxtapositioned” to the area where prescriptions are dispensed. It has to be in public view, close to the dispensing of the medication.

Senator THURMOND. Is there any requirement that the pharmacist post that to consumers when they come in to buy drugs?

Mr. DENUZZO. It is there every minute that pharmacy is open. That poster is available for the patient to see, and the poster must be updated. If the price changes, then the poster has got to change.

Senator THURMOND. Now, is that the law of New York?

Mr. DENUZZO. Yes, sir.

Senator THURMOND. In other words, the pharmacies in New York have to post this price list that you put out?

Mr. DENUZZO. It is of the top 150 drugs and the price is the price that they charge for a prescription. This information is fairly common information. It is picked up by others and is in distribution.

They do not have to post this in their pharmacy. They have to post the price that they will charge for the top 150 prescription drugs that are used in New York State.

Senator THURMOND. They have to post the price of a patented drug and then a generic drug that is equivalent?

Mr. DENUZZO. If there is one available, then there will be dual posting. The brand name will be on the top and below it will be the name of the generic counterpart and the price for both.

Senator THURMOND. Do you know how many States have that requirement?

Mr. DENUZZO. Honestly, no.

Senator THURMOND. Thank you very much.

Mr. DENUZZO. You are welcome.

Senator THURMOND. Thank you, Mr. Chairman.

Senator METZENBAUM. If you will submit that statement that has to be posted, we will include it in the record.

Mr. DENUZZO. You would like a copy of the price posting?

Senator METZENBAUM. Yes.

Mr. DENUZZO. I will have to mail it to you.

[Prescription price lists follow:]

GENERIC DRUGS

COMPARE THE SAVINGS

Strength/ Dosage	Quantity	Brand Name Generic Name	Brand Name Price	Average Generic Price
25 mg/ 25 mg	60	Aldactazide Spironolactone/ Hydrochlorothiazide	\$20.89	\$ 6.31
250 mg	90	Aldomet Methyldopa	\$27.75	\$20.63
250 mg	30	Amoxil Amoxicillin	\$ 9.24	\$ 5.86
12.5 mg	50	Antivert Meclizine HCl	\$12.66	\$ 2.66
10 mg	36	Alaxax Hydroxyzine	\$14.48	\$ 5.56
1 mg	30	Ativan Lorazepam	\$14.85	\$ 8.18
800 mg/ 160 mg	20	Bactrim DS Sulfamethoxazole/ Trimethoprim	\$17.18	\$ 9.78
50 mg	30	Benadryl Diphenhydramine HCl	\$ 5.60	\$ 1.95
0.1 mg	60	Catapres Clonidine HCl	\$19.01	\$ 6.93
1 mg	15	Cogentin Benzotropine Mesylate	\$ 2.52	\$ 1.95
10 mg	30	Compazine Prochlorperazine	\$15.95	\$ 5.86
30 mg	30	Dalmane Flurazepam	\$12.41	\$10.44
100 mg	36	Darvocet N Propoxyphene N/APAP	\$15.75	\$10.80
65 mg	50	Darvon Compound Propoxyphene HCl/ASA	\$14.28	\$ 3.60
0.75 mg	18	Decadron Dexamethasone	\$ 9.58	\$ 1.95
250 mg	60	Diabinese Chlorpropamide	\$31.96	\$ 3.32
tablet	60	Donnatal Belladonna Alkaloids/ Phenobarbital	\$ 4.13	\$ 1.95
400 mg	28	E.E.S. Erythromycin Ethylsuccinate	\$ 8.65	\$ 8.35
25 mg	40	Elavil Amitriptyline	\$11.79	\$ 1.95
tablet	50	Empirin w/ Codeine Aspirin/Codeine	\$10.48	\$ 6.46
tablet	40	Fiorinal Butalbital/Aspirin/Caffeine	\$10.52	\$ 1.95
250 mg	30	Flagyl Metronidazole	\$32.75	\$ 7.60
2% ophthalmic solution	5 ml	Garamycin Gentamicin Sulfate	\$10.56	\$ 8.21
1 mg	30	Haloid Haloperidol	\$11.39	\$ 9.41
25 mg	50	Hygroton Chlorthalidone	\$17.37	\$ 4.74

Strength/ Dosage	Quantity	Brand Name Generic Name	Brand Name Price	Average Generic Price
1% cream	30 gm	Hytone Hydrocortisone	\$ 6.06	\$ 2.01
40 mg	100	Inderal Propranolol HCl	\$34.60	\$11.46
25 mg	40	Indocin Indomethacin	\$19.43	\$11.97
10 mg	100	Isordil Isosorbide Dinitrate	\$15.66	\$ 2.13
40 mg	50	Lasix Furosemide	\$ 9.13	\$ 4.83
10 mg	36	Librium Chlordiazepoxide HCl	\$12.50	\$ 1.95
tablet	24	Lomolil Diphenoxylate HCl/ Atropine Sulfate	\$ 8.50	\$ 1.95
1 mg	120	Lunel Sodium Fluoride	\$ 7.70	\$ 2.22
25 mg	90	Mellari Thioridazine HCl	\$29.61	\$22.26
600 mg	60	Motrin Ibuprofen	\$21.61	\$ 9.70
oral suspension	60 ml	Mycostatin Nystatin	\$23.01	\$ 9.48
tablet	30	Naidecon PPA/Phenylephrine/Phenyl- toloxamine/Chlorpheniramine	\$16.88	\$ 1.95
tablet	60	Percocet Acetaminophen/ Oxycodone HCl	\$23.21	\$10.79
tablet	60	Percodan Aspirin/Oxycodone HCl/ Oxycodone Terephthalate	\$23.09	\$10.79
6.25 mg/ 10 mg	120 ml	Phenergan w/ Codeine Promethazine w/ Codeine	\$ 4.09	\$ 2.31
tablet	100	Poly-Vi-Flor Multivitamins w/ Fluoride	\$12.99	\$ 5.06
10 mg	60	Reglan Metoclopramide HCl	\$21.77	\$ 8.20
30 mg	30	Reston Temazepam	\$13.62	\$10.28
100 mg	30	Tolnase Tolazamide	\$ 7.63	\$ 5.20
tablet	100	Tri-Vi-Flor Vitamin A, C, D, & Fluoride	\$11.26	\$ 3.03
tablet	30	Tylenol w/ Codeine APAP/Codeine 30 mg	\$ 5.31	\$ 2.88
5 mg	50	Valium Diazepam	\$21.44	\$ 5.82
250 mg	40	V-Clin K Penicillin VK	\$ 7.79	\$ 2.87
100 mg	20	Vibramycin Doxycycline Hyclate	\$50.22	\$ 9.94
100 mg	60	Zyloprim Allopurinol	\$ 9.61	\$ 3.86

Prices may vary from store to store and are subject to change.

PRESCRIPTION PRICE LIST

INSTRUCTIONS

1. This pharmacy's prices for the most frequently prescribed drugs and in the quantities most commonly prescribed are listed below. Look on the list for the drug you doctor has prescribed for you. The price for any prescription not listed will be provided upon request and upon the presentation of a prescription for pricing.

2. Check your Prescription. The pharmacist is required to dispense a less expensive generic drug in place of a brand name drug if your doctor signs the prescription over the right-hand signature line marked "substitution permissible" and the generic drug is found in the New York equivalent drug list.

3. All generic drug names are printed in quotes. The price of the brand-name drug is listed on top line; the generic or less-expensive drug price is listed on bottom line.

Drug	Quantity	Price
"Acetaminophen with Codeine Phosphate" 30 mg tab [III]	20	
Aldomet* tab 250 mg	100	
"Methyldopa"	100	
Aldomet* tab 500 mg	60	
"Methyldopa"	60	
Aldoril* 25 tab	100	
Alupent* Metered Dose Inhaler	15 ml	
"metaproterenol sulfate"	15 ml	
Amoxil* cap 250 mg	20	
"Amoxicillin"	20	
Amoxil* suspension 125 mg/ 5ml	100 ml	
"Amoxicillin"	100 ml	
Amoxil* suspension 250 mg/ 5 ml	100 ml	
"Amoxicillin"	100 ml	
Anaprox* tab 275 mg	30	
"naproxen sodium"	30	
Armour* Thyroid tab 60 mg	100	
"thyroid"	100	
Atarax* tab 25 mg	30	
"Hydroxyzine Hydrochloride"	30	
Ativan* tab 1 mg [IV]	30	
"Lorazepam"	30	
Bactrim™ DS tab	20	
Beepen* VK tab 250 mg	40	
"Penicillin V Potassium"	40	
Benadryl* Kapseals* 50 mg	30	
"Diphenhydramine Hydrochloride"	30	
Brethine* tab 2.5 mg	100	
"terbutaline sulfate"	100	
Captopril* tab 25 mg	60	
"captopril"	60	
Cardizem* tab 30 mg	60	
"diltiazem hydrochloride"	60	
Catapres* tab 0.1 mg	60	
"clonidine hydrochloride"	60	
Ceclor* Pulvules* 250 mg	20	
"cefaclor"	20	
Clinoril* tab 200 mg	30	
"sulindac"	30	
Corgard* tab 40 mg	30	
"nadolol"	30	
Cortisporin* ophth susp	7.5 ml	
Coumadin* tab 5 mg	30	
"Warfarin Sodium"	30	
Dalmane* cap 15 mg [IV]	30	
"Flurazepam Hydrochloride"	30	
Dalmane* cap 30 mg [IV]	30	
"Flurazepam Hydrochloride"	30	
Darvocet-N* 100 tab [IV]	30	
"Propoxyphene Napsylate, Acetaminophen"	30	

Drug	Quantity	Price
Demulen™ 1/35.....	21	
Demulen™ 1/35.....	28	
Desyrel® tab 50 mg.....	30	
"trazadone hydrochloride".....	30	
Diabinese® tab 250 mg.....	30	
"Chlorpropamide".....	30	
Dilantin® Kapseals® 100 mg.....	100	
"Phenytoin Sodium, Extended".....	100	
"Dipyridamole" tab 50 mg.....	60	
Dolobid® tab 500 mg.....	20	
"diflunisal".....	20	
Donnatal® tab.....	100	
Dyazide® cap.....	30	
E.E.S. 400® Filmtabs®.....	20	
"Erythromycin Ethylsuccinate".....	20	
E.E.S. 400® Liquid.....	100 ml	
"Erythromycin Ethylsuccinate".....	100 ml	
Elavil® tab 25 mg.....	60	
"Amitriptyline hydrochloride".....	60	
Empirin® with Codeine No. 3 tab [III].....	20	
E-Mycin® tab 250 mg.....	20	
"Erythromycin base".....	20	
Entex® LA tab.....	15	
"phenylpropanolamine, guaifenesin".....	15	
ERYC® cap 250 mg.....	20	
"erythromycin".....	20	
Erythrocin® Filmtab® 250 mg.....	20	
"Erythromycin Stearate".....	20	
Erythromycin Base® tab 250 mg (see also E-MYCIN® 250 mg).....	20	
Feldene® cap 20 mg.....	15	
"piroxicam".....	15	
Fiorinal® tab [III].....	30	
"Butalbital, Aspirin, Caffeine".....	30	
Fiorinal® with Codeine No. 3 cap [III].....	20	
Flexeril® tab 10 mg.....	30	
"cyclobenzaprine hydrochloride".....	30	
Halcion® tab 0.25 mg [IV].....	30	
"triazolam".....	30	
Haldol® tab 1 mg.....	60	
"haloperidol".....	60	
"Hydrochlorothiazide" tab 50 mg (see also HYDRODIURIL®).....	30	
Hydrodiuril® tab 50 mg.....	30	
"Hydrochlorothiazide".....	30	
Hygroton® tab 25 mg.....	30	
Chlorthalidone.....	30	
Hygroton® tab 50 mg.....	30	
"Chlorthalidone".....	30	
Inderal® tab 10 mg.....	100	
"Propranolol Hydrochloride".....	100	
Inderal® tab 20 mg.....	100	
"Propranolol Hydrochloride".....	100	
Inderal® tab 40 mg.....	100	
"Propranolol Hydrochloride".....	100	
Inderal® tab 80 mg.....	60	
"Propranolol Hydrochloride".....	60	
Indocin® cap 25 mg.....	60	
"Indomethacin".....	60	
Indocin® cap 50 mg.....	30	
"Indomethacin".....	30	
Isordil® Oral Titradose® 10 mg.....	100	
"isosorbide dinitrate".....	100	
K-Tab® Filmtab®.....	60	
"potassium chloride".....	60	
Keflex® Pulvules® 250 mg.....	20	
"cephalexin".....	20	

Drug	Quantity	Price
Keflex® Pulvules* 500 mg	20	20
"cephalexin"	20	20
Lanoxin® tab 0.125 mg	100	100
"digoxin"	100	100
Lanoxin® tab 0.25 mg	100	100
"digoxin"	100	100
Lasix® tab 20 mg	30	30
"Furosemide"	30	30
Lasix® tab 40 mg	30	30
"Furosemide"	30	30
Ledercillin® VK tab 250 mg	40	40
"Penicillin V Potassium"	40	40
Lidex® cream 0.05%	15 gm	15 gm
"Fluocinonide"	15 gm	15 gm
LO/Ovral® tabs	21	21
LO/Ovral® tabs	28	28
Lopressor® tab 50 mg	30	30
"metoprolol tartrate"	30	30
Lotrimin® cream 1%	15 gm	15 gm
"Clotrimazole"	15 gm	15 gm
Macrochantin® cap 50 mg	30	30
"nitrofurantoin macrocrystals"	30	30
Maxzide® tab	30	30
Mellaril® tab 25 mg	100	100
"thioridazine hydrochloride"	100	100
Mellaril® tab 50 mg	30	30
"thioridazine hydrochloride"	30	30
Micro-K Extencaps®	60	60
"potassium chloride"	60	60
Minipress cap 2 mg	60	60
"prazosin hydrochloride"	60	60
Moduretic® tab	30	30
Monistat® 7 vaginal cream	45 gm	45 gm
"miconazole nitrate"	45 gm	45 gm
Motrin® tab 400 mg	60	60
"ibuprofen"	60	60
Motrin® tab 600 mg	30	30
"ibuprofen"	30	30
Naldecon® tab	30	30
Nalfon® tab 600 mg	30	30
"fenoprofen calcium"	30	30
Naprosyn® tab 375 mg	30	30
"naproxen"	30	30
Naprosyn® 500 mg	30	30
"naproxen"	30	30
Nicorette®	96	96
"nicotine polacrilex"	96	96
Nitrostat® tab 0.4 mg	100	100
"nitroglycerin"	100	100
Nordette® tab	21	21
Nordette® tab	28	28
Norinyl® 1 + 35	21	21
Norinyl® 1 + 35	28	28
Norinyl® 1 + 50	21	21
Norinyl® 1 + 50	28	28
Omnipen® cap 250 mg	20	20
"Ampicillin"	20	20
Omnipen® cap 500 mg	20	20
"Ampicillin"	20	20
Ortho-Novum® 1/35 tab	21	21
Ortho-Novum® 1/35 tab	28	28
Ortho-Novum® 1/50 tab	21	21
Ortho-Novum® 1/50 tab	28	28
Ortho-Novum® 7/7/7	21	21
Ortho-Novum® 7/7/7	28	28

Drug	Quantity	Price
Ortho-Novum* 10/11 tab.....	21	
Ortho-Novum* 10/11/ tab.....	28	
Ovral* tab.....	21	
Pen-Vee* K tab 250 mg.....	40	
"Penicillin V Potassium".....	40	
Percocet* tab [II].....	20	
"Oxycodone with Acetaminophen".....	20	
Percodan* tab [II].....	20	
"Oxycodone with Aspirin".....	20	
Persantine* tab 25 mg.....	60	
"dipyridamole".....	60	
Phenergan* with Codeine [V].....	120 ml	
"Promethazine Hydrochloride, Codeine".....	120 ml	
Polymox* cap 250 mg.....	20	
"Amoxicillin".....	20	
Premarin* tab 1.25 mg.....	21	
"conjugated estrogens".....	21	
Procardia* cap 10 mg.....	90	
"nifedipine".....	90	
Proventil* Inhaler.....	17 gm	
"albuterol".....	17 gm	
Provera* tab 10 mg.....	10	
"medroxyprogesterone".....	10	
Reglan* tab 10 mg.....	30	
"Metoclopramide Hydrochloride".....	30	
Restoril* cap 15 mg [IV].....	30	
"Temazepam".....	30	
Rufen* tab 400 mg.....	60	
"Ibuprofen".....	60	
Rufen* tab 600 mg.....	30	
"Ibuprofen".....	30	
Sepra* DS tab.....	20	
Sinequan cap 25 mg.....	30	
"doxepin".....	30	
Slow-K* tab 600 mg.....	60	
"potassium chloride".....	60	
Synthroid* tab 0.1 mg.....	100	
"levothyroxine sodium".....	100	
Synthroid* tab 0.2 mg.....	100	
"levothyroxine sodium".....	100	
Tagamet* 300 mg.....	60	
"cimetidine".....	60	
Tegretol* tab 200 mg.....	100	
"carbamazepine".....	100	
Tenormin* tab 50 mg.....	30	
"atenolol".....	30	
"Tetracycline Hydrochloride" cap 250 mg.....	20	
Theo-Dur* s.a. tab 200 mg.....	60	
"theophylline anhydrous".....	60	
Timoptic* 0.5 percent.....	5 ml	
"timolol maleate".....	5 ml	
Tolinase* tab 250 mg.....	30	
"Tolazamide".....	30	
Transderm-Nitro* 5 mg/24 hr.....	30	
"nitroglycerin".....	30	
Tranxene* cap 3.75 mg [IV].....	60	
"clorazepate dipotassium".....	60	
Tranxene* cap 7.5 mg [IV].....	60	
"clorazepate dipotassium".....	60	
Triavil* 2-25 tab.....	60	
Tylenol* with Codeine No. 3 tab [III].....	20	
"Acetaminophen with Codeine" 30 mg.....	20	
Tylenol* with Codeine No. 4 tab [III].....	20	
"Acetaminophen with Codeine" 60 mg.....	20	
Valisone cream 0.1 percent.....	15 gm	

Drug	Quantity	Price
"Betamethasone Valerate"	15 gm	
Valium* tab 2 mg [IV]	90	
"Diazepam"	90	
Valium* tab 5 mg [IV]	90	
"Diazepam"	90	
Valium* tab 10 mg [IV]	30	
"Diazepam"	30	
Ventolin* Inhaler	17 gm	
"albuterol"	17 gm	
Vicodin* tab [III]	20	
"Hydrocodone with Acetaminophen"	20	
Xanax* tab 0.5 mg [IV]	30	
"alprazolam"	30	
Zantac* tab 150 mg	30	
"ranitidine hydrochloride"	30	
Zyloprim* tab 100 mg	100	
"Allopurinol"	100	
Zyloprim* tab 300 mg	30	
"Allopurinol"	30	

SPECIAL PRICING POLICIES

The above prices do not apply to Medicaid prescriptions reimbursed at a lower rate under Medicaid reimbursement schedules.

Consult your pharmacist for the selection of the most economical drug product available to fill your doctor's prescription.

The posting of this list is required by all pharmacies pursuant to Section 6826 of the Education Law.

Prepared and distributed by the Board of Pharmacy, State Education Department, Cultural Education Center, Room 3035, Albany, New York 12230.

Complaints may be sent to the Office of Professional Discipline, State Education Department, 622 Third Avenue, New York, New York 10017 or call Toll Free State-wide 1-800-442-8106

I, _____ supervising pharmacist of _____ do hereby certify that this is a list of the prices charged currently by this pharmacy.

Effective date: June 15, 1986.

Senator METZENBAUM. Thank you very much, Professor DeNuzzo. Your testimony has been very helpful. Thanks a lot.

Mr. DeNuzzo. Thank you.

[Prepared statement follows:]

Good Morning! My name is Rinaldo V. DeNuzzo. I am a pharmacist and educator from Albany, New York, with an academic appointment as a Professor of Pharmacy at the Union University College of Pharmacy and a position as a Consultant Pharmacist to the New York State Department of Health, Office of Health Systems Management. I teach pharmacy law, marketing, and management. My responsibilities with the Department of Health include an appointment as chair of the Commissioner's Technical Pharmacy Advisory Committee. TPAC makes recommendations to the Commissioner or his designee concerning the additions of or deletions of drugs made available to prescribers in the medical assistance program within a cost containment charge. This puts me in contact with representatives of the "brand name" drug industry.

I am the author and originator of the "Annual Prescription Survey" which began in 1956, and I am currently accumulating data for a 32nd report. I do, or have done, other forms of market research with respect to the delivery of prescription and non-prescription drugs to patients in the ambulatory or out-patient environment and to residents in skilled nursing facilities. These research activities presented me with an opportunity to assist New York in the implementation in 1978 of a special two-signature line prescription blank which was designed to increase the use of less expensive therapeutically equivalent multisource products (generics) for brand name drugs. Among my many activities at that time was to direct the publication of a paper back handbook titled Safe, Effective, and Therapeutically Equivalent Prescription Drugs to project potential consumer savings, and measure the success of this legislation.

Testimony of Rinaldo V. DeNuzzo, Professor, Union University College of Pharmacy, Albany, New York, to the Subcommittee on Antitrust, Monopolies, and Business Rights of the Committee on Judiciary of the United States Senate, October 21, 1987.

I will address prescription drugs. They are unique in that they are directed consumer goods. This means that the user of the good is "directed" to do so by the prescriber who is truly the consumer. We have a situation where one person makes a purchasing decision for another person, and I am of the opinion, often with scant regard for the costs involved and with no personal economic risk. In addition, the universe of FDA approved prescription drug products currently includes some 9,429 drugs of which 7,306 (77.5%) are available from multiple sources, and 6,309 (86.4%) of them have therapeutically equivalent products (generics) in the market place.

With these FDA statistics and the information I accumulate annually about the prescription drug market, there is currently more than 500 million of 800 million new scripts dispensed annually for which there are multisource products. I estimate that this market is in excess of 7 billion dollars. It is a sizeable market to retain, gain, or lose.

Multisource drugs (generic and brand name) may differ in color, size, shape, or flavoring. The major difference, however, is the price which consumers pay. On the average, generic drugs cost about 50 percent less than therapeutically equivalent brand name drugs. This is possible because generics are no longer the exclusive property of the original developer or patent holder, and a manufacturer can produce them at a lower cost, passing savings on to the true consumer.

I am of the opinion that many consumers wish to enjoy the savings associated with multisource (generic) drug use; however, they are confused by the issues raised by the brand name drug industry. These issues serve them to maintain market exclusivity over drug products now in public domain. Consumers want to know what a generic drug is. They want to know the difference

between generic and branded drugs. They also want assurances that generic product interchange is safe and will not cause potential harm. Prescribers are concerned that they will be subject to liability if they permit the use of a "questionable quality" legally marketed therapeutically equivalent multisource product in place of a brand name drug.

To allay concerns of the consumer, pharmacist, and prescriber, the Federal Food and Drug Administration recently prepared an article titled "FDA Speaks Out About Generic Drug Quality," which was published by the National Association of Boards of Pharmacy last year. It contained ten myths currently raised by brand name firms, directly or through intervening sources used to discourage the use of generic drugs. In each case it states the facts.

New York State has an ongoing educational program which serves to provide the facts to consumers of drug products. I took an active role in this endeavor by staffing an informational booth at the 1987 New York State Fair for two weekends during August and September. The state provides all pharmacies and prescribers with the latest information concerning the availability of multisource therapeutically equivalent products. To relieve the fears of prescribers who permit generic drug use, a new state law, effective July 1, 1987, "holds harmless" all writers from any civil liability arising solely from the authorization of substitution by a pharmacist of a drug product which is therapeutically equivalent. Yet writers are still fearful of law suits.

In spite of all the attempts to educate the public, issues continue to surface which create doubt in the minds of the prescriber and patient alike. As an example, I received two letters within the past eight days from neurologists, unknown to me, concerning the impending implementation of the health care financing administration regulation which will set "specific

upper limits for multiple source and other drugs" on October 29, 1987. In my position as chair of the TPAC, I often receive multiple mailings within a short time span. Quite often the only difference in each letter is the name and address of the sender. I call this an orchestrated communication.

These letters are slightly different; however, the message is the same. These neurologists claim that the use of generic drugs for brand names may, and the word is used frequently, not have the same bioavailability properties and absorption, may result in "break through" seizures, may lead to the need for further hospitalization and readjustment of medication, and may increase costs which will outweigh the economic benefits enjoyed when using the generic version.

A controlled circulation journal mailed to diabetic patients contained an article about diabetes. It was very informative about the disease; however, a subtle message was also given. The reader was advised that the long term effects of generic drug use in the body was unknown. Why take the chance.

This pharmacist-educator is truly concerned about the brand name drug industry which has the capability to conduct meaningful research and submit detailed data leading to a successful new drug application for a safe and effective product. However, on occasion some drug companies will attempt to achieve marketing objectives by resorting to unsubstantiated claims. There has been sufficient time for these companies to document the perceived problems associated with generic drug interchange for a brand name product. It is time for the truth to be known.

Senator METZENBAUM. Our next witnesses are Gerald Mossinghoff, President of the Pharmaceutical Manufacturers Association, of Washington, who I understand is accompanied by Dr. Jennings. We are very happy to have you with us, Mr. Mossinghoff.

Mr. Mossinghoff, as I understand it, you are here speaking in behalf of the organization, but not on behalf of any specific or any group of companies, as such. Is that correct?

STATEMENT OF GERALD J. MOSSINGHOFF, PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION, WASHINGTON, DC, ACCOMPANIED BY JOHN JENNINGS, VICE PRESIDENT, SCIENCE AND TECHNOLOGY, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

Mr. MOSSINGHOFF. That is correct, Mr. Chairman. The Pharmaceutical Manufacturers Association represents more than a hundred of the brand-name, research-based pharmaceutical companies in the United States, but as president of that association, my role is to represent the industry on broad industry issues and not necessarily individual companies on specific issues, and I do appreciate your noting that.

Senator METZENBAUM. I think that is important because the Chair actually wanted, as I previously stated, to get Ayerst and Pfizer or any other company who wanted to testify, because I believe that a chairman has a responsibility to provide a balanced hearing.

I am sorry that they decided not to appear, or that any other companies failed to indicate that they desired to appear. Had they done so, we would have been perfectly willing to hear from them.

Please proceed, Mr. Mossinghoff. We are happy to have you with us, and I understand you are accompanied by Dr. Jennings, is that right?

Mr. MOSSINGHOFF. That is right, Mr. Chairman. Dr. Jennings is PMA's vice president for Science and Technology.

Senator METZENBAUM. Mr. Mossinghoff, since I think you are the only witness opposed to the other side of this issue, how much time do you think you need in order to be fair to you?

Mr. MOSSINGHOFF. I think five minutes would be adequate for me to cover the summary points of my statement, Mr. Chairman.

Senator METZENBAUM. All right. If you need a couple minutes more, I want to be fair. I do not want to cut you off, so please proceed.

Mr. MOSSINGHOFF. Thank you.

Mr. Chairman and Senator Thurmond, I would like to make the following points in the summary of my statement. First, let me say that our way of life in the United States would be unimaginable without the modern medicines discovered and developed by PMA companies through their research and development.

During 1986, PMA companies invested \$4.6 billion in research and development, an increase of 12 percent over 1985. People are living longer, healthier, and more productive lives as a direct result of that investment.

In recent years, the costs of providing health care and the prices charged have risen substantially. The same is true for prescription

drugs, but modern prescription drugs are a very good value. Prescription drug prices have remained below the Consumer Price Index ever since that index was set in 1967 at 100, and drug prices today are less than two-thirds of the overall price index for medical care. I have provided a chart in my testimony, Figure 1, that shows the relationships of those three indices.

Secondly, research and development are the hallmarks of PMA member companies. Their investment in R&D continues to double every 5 years. That is shown in figure 2 in my statement.

This year, the industry will spend \$5 billion in discovering and developing new life-saving medicines, at an average cost of \$125 million for each new drug. There would, of course, be few generic drugs without the huge investment by the research-based pharmaceutical industry in discovering and developing new drugs and in educating physicians and other health care professionals to use them properly and effectively.

Third, the industry is investing an increasingly higher percentage of sales, currently 15 percent of sales, to finance its growing investment in research and development. Measuring increases in R&D expenditures the same way as we measure the Consumer Price Index or the drug price index, the index for research and development conducted by PMA companies now stands at over 1,000, 3½ times the prescription drug consumer price index. That is shown in figure 3 of my statement.

There obviously is a place in the U.S. free market economy for generic copies of pioneer drugs whose patents have expired. I might add, Mr. Chairman, that before I came to PMA, PMA was involved in the compromise that you mentioned, the ANDA/Patent Term Restoration legislation, and that does permit an additional five years to be added to a drug's patent life to accommodate or make up for the time lost in premarket clearance by the Food and Drug Administration.

But in no instance can the time of a PMA patent so extended exceed 14 years. That is a specific statutory limit in the law, which is 3 years less than the normal 17 years that other manufacturers and inventors enjoy under their patents.

PMA is concerned, however, that generic drugs have been approved for marketing that are not, in practice, therapeutically equivalent to the pioneer products. Despite the claim of the Food and Drug Administration, for which I have great admiration, that it is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the agency as bioequivalent, there are many examples where generic drugs produce different clinical results than pioneer products.

The details of nine specific reports are set forth in the appendix to my statement, which I would ask that the committee put in the record of this hearing.

Senator METZENBAUM. It will be included in the record.

[Information follows:]

APPENDIX TO
TESTIMONY OF

GERALD J. MOSSINGHOFF
PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

SUBCOMMITTEE ON ANTITRUST, MONOPOLIES AND BUSINESS RIGHTS
COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

OCTOBER 21, 1987

CASE REPORT #1 (1987) -- Primidone (rated AB*); 4 sources;
First marketed 1954

A 16 year old female with severe cerebral palsy, mental retardation, microcephaly and seizures since birth had been treated with daily doses of 500 mg Mysoline (primidone) and 4 mg Klonopin (clonazepam) for 9 years during which time her usual seizure frequency was 1-2 per week. Bolar's generic primidone was substituted and within 3 weeks, her seizure frequency rose dramatically. She was returned to Mysoline and her seizure frequency decreased to baseline.

Three months later, the patient was hospitalized for other problems which were quickly resolved, but remained hospitalized for a prolonged period of time due to problems with the antiepileptic medications. During her hospitalization, she was switched to Bolar's generic primidone and a precipitous drop in blood level concentration was noted. Upon admission (while on Mysoline) her primidone blood levels were 10.8 mg/l and phenobarbital concentration was 19.1 mg/l; after 6 days on generic primidone, the primidone levels dropped to 5.1 mg/l and phenobarbital dropped to 15.9 mg/l. Phenobarbital is a product of primidone biotransformation. Despite an increase in dosage of generic primidone from 500 to 625 mg, the blood levels continued to drop and the patient suffered more frequent seizures. After 10 days on generic primidone, she was returned to Mysoline therapy and her blood levels and seizure frequency returned to baseline. The hospital pharmacy policy was changed to prevent generic primidone substitution.

NOTE: Case report was published in the Journal of the American Medical Association (attached).

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

Increased Seizure Frequency With Generic Primidone

Elaine Wyllie, MD; C. E. Pippenger, PhD; A. David Rothner, MD

GENERIC drugs produced by different pharmaceutical companies may have different rates of extent of absorption.¹⁻⁴ This is particularly important to epileptic patients, because most of the antiepileptic medications have low therapeutic indexes. If a patient switches from an antiepileptic preparation with fairly complete absorption to one with less complete absorption, then the serum drug concentration may drop and the patient could have an increased frequency of seizures. If a patient is switched in the other direction, from a less well-absorbed preparation to one that is better absorbed, then the serum concentrations may rise and the patient could have symptoms of toxic effects. Even if the new product has the same completeness of absorption, there may still be a faster or slower rate of absorption that could affect dosing schedules.

See also p 1200.

These problems have occurred for patients with epilepsy. Previous reports have shown differences in bioequivalence for preparations of phenytoin sodium⁵⁻⁸ and phenobarbital,^{9,10} and we describe a patient who had problems with generic primidone (Bolar Pharmaceutical Co, Copiague, NY). This new case is of concern because of the recent increase in availability of generic drugs

since implementation of the Drug Price Competition and Patent Term Restoration Act of 1984.¹¹ In defense of the new regulations, the Food and Drug Administration (FDA) stated it "is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the Agency as bioequivalent."¹² Our patient provides such a case.

Report of a Case

A 15-year-old girl had severe quadriparetic cerebral palsy, mental retardation, microcephaly, and seizures since birth. Seizures were generalized tonic-clonic, atonic, and myoclonic, and an electroencephalogram showed slow spike-and-wave complexes and slowing of background rhythms. Antiepileptic medications included primidone (Mysoline, Ayerst Laboratories, New York) 500 mg (17 mg/kg) per day and clonazepam (Klonopin, Hoffmann-La Roche Inc, Nutley, NJ) 4 mg (0.14 mg/kg) per day, and her usual seizure frequency was one to two seizures per week.

The patient had been taking the same antiepileptic medications for nine years, when she was switched to a less expensive form of generic primidone (Bolar Pharmaceutical Co, Copiague, NY). This form, like Mysoline, is listed in the FDA's most recent published list of approved drug products.¹³ Within three weeks, there was a dramatic rise in seizure frequency, so she was switched back to Mysoline. With this single change, the seizure frequency decreased to baseline. Serum drug concentrations were not measured.

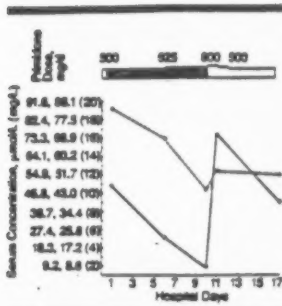
The patient's condition remained stable until three months later, when she was admitted to the hospital for feeding

problems. These problems were quickly resolved, but a prolonged hospitalization was required because of problems with the antiepileptic medication. Before admission, she was taking her usual doses of Mysoline and Klonopin, and trough serum antiepileptic medication concentrations were similar to those during the last year. During the hospitalization, however, she received generic primidone (Bolar) instead of Mysoline, and there was a precipitous drop in morning trough serum primidone and phenobarbital concentrations as determined by fluorescence polarization immunoassays (Abbott-TDX, Abbott Laboratories, North Chicago, Ill). On the morning after admission, the trough primidone concentration was 49.5 $\mu\text{mol/L}$ (10.8 mg/L), and the phenobarbital concentration was 82.2 $\mu\text{mol/L}$ (19.1 mg/L); however, after six days of receiving generic primidone, the morning trough primidone concentration was 23.4 $\mu\text{mol/L}$ (5.1 mg/L), and the phenobarbital concentration was 68.5 $\mu\text{mol/L}$ (15.9 mg/L) (Figure).

The reason for the decrease in the serum primidone and phenobarbital concentrations was not immediately clear to the patient's physicians. It was known that the patient swallowed every dose of medication, because she was observed each time by nurses. The physicians incorrectly assumed that the patient was still receiving Mysoline when, in fact, she was receiving generic primidone (Bolar), because the hospital pharmacy had acted independently in making the generic substitution. On day 6, the dose of generic primidone was increased from 500 to 625 mg/d, but despite this, the serum concentration continued to drop and the patient had

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Serum concentrations of primidone (solid line) and phenobarbital (broken line) decreased when patient was switched from primidone (Mysoline, Ayerst Laboratories, New York, shaded bar at top) to generic primidone (Bolar Pharmaceuticals Co., Copleague, NY, crosshatched bar at top). For serum concentrations, first number refers to primidone SI unit value; second number, phenobarbital SI unit value; and third number in parentheses, milligrams per liter.

more frequent seizures. On day 10, the serum primidone concentration was less than 9.2 µmol/L (2.0 mg/L), and the serum phenobarbital concentration was 44.8 µmol/L (10.4 mg/L). In contrast, the serum clonazepam concentration remained unchanged at 0.05 µmol/L (15 ng/mL).

On day 10, the patient's primidone tablets were examined, and it became clear that the patient had been receiving generic primidone. From then on, administration of the generic primidone was discontinued, and she received only Mysoline. On day 11, after a loading dose of 800 (28 mg/kg), the serum primidone concentration was 75.1 µmol/L (16.4 mg/L), and the serum phenobarbital concentration was 54.7 µmol/L (12.7 mg/L). After six days of receiving Mysoline, 500 mg (17 mg/kg) per day, the primidone concentration was 41.2 µmol/L (9.0 mg/L), the phenobarbital concentration was 51.7 µmol/L (12.0 mg/L), and the patient's seizure frequency returned to baseline. The hospital pharmacy policy was changed to prevent generic primidone substitutions, and a report was filed with the FDA.

Comment

Our patient had problems twice when she was switched from primidone (Mysoline) to generic primidone (Bolar). With both episodes, the seizure frequency increased. With the second episode, the trough serum primidone and phenobarbital concentrations dropped precipitously. The primidone concen-

tration dropped because the generic drug was not being absorbed to any significant degree, and the phenobarbital concentration dropped because of diminishing amounts of primidone available for biotransformation.¹⁸ If the generic preparation had been used for another several days, then the serum phenobarbital concentration would probably have also dropped to zero. The two primidone preparations were clearly not bioequivalent in our patient, even though both were approved by the FDA.¹⁹ This case demonstrates that approval by the FDA does not guarantee bioequivalence.

The biologic inequivalence of the generic primidone was not reflected by dissolution testing from the manufacturer (Bolar) or the distributor (UDL Laboratories, Inc., Rockford, Ill). In response to our requests, Bolar and UDL Laboratories, Inc., reevaluated the in vitro dissolution data and reported that results for the appropriate lot were "within standard specifications." Details of these data, and the bases for Bolar's standard specifications, were not provided. In this case, the standard in vitro dissolution testing was inadequate to ensure bioequivalence.

There have been two reported studies that compared primidone preparations in vivo. Borst and Lockwood²⁰ studied nine epileptic patients who each took two preparations from different Canadian drug manufacturers, and Biemann et al²¹ studied 12 epileptic patients who each took two lots of Mysoline from Ayerst Laboratories. In both studies, patients took each preparation for two weeks. Borst and Lockwood²⁰ found no significant differences in the mean serum primidone or phenobarbital concentrations with either preparation, but Biemann et al²¹ found that one of the lots of Mysoline gave significantly lower mean serum phenobarbital concentrations and also had a significantly slower in vitro dissolution time. The group data from Biemann et al²¹ gave evidence that primidone bioavailability might vary from lot to lot; but they did not permit comparison of the two lots in specific individuals. Our case demonstrates that primidone preparations from different manufacturers can have different bioavailability, and that the difference can cause clinical problems.

Unfortunately, problems with generic substitution cannot be totally eliminated even with the most comprehensive in vivo and in vitro lot-to-lot bioequivalence testing. Such testing could reduce, but not eliminate, the risk of inappropriate substitution for a specific individual. Therefore, the only way

to ensure appropriate therapy after generic substitution is to rehydrate the patient. The clinical status must be closely monitored for increased seizures or toxic drug effects, and the serum drug concentration should be measured at the anticipated time of steady state. We agree with Hwang et al¹ that product substitutions should be cautiously considered in patients who have already been titrated and maintained on an antiepileptic preparation.

We wish to thank Hans Liders, MD, PhD, for reviewing the manuscript and Nancy M. Staats for secretarial help.

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CASE REPORT #2 (1987) -- Carbamazepine (rated AB*); 5 sources;
First marketed 1968

Three separate patients were reported to have suffered breakthrough seizures after being switched from Tegretol (carbamazepine) to a generic preparation.

A 51 year old man who had been clinically stable and seizure free for 9 months on daily doses of 1200 mg Tegretol and 200 mg phenytoin, was switched to generic carbamazepine and within 5 days suffered a seizure. After 6 seizures in 3 weeks, he was returned to Tegretol and has remained seizure free for 6 months.

A 46 year old woman who had been seizure free for 3 months on 1600 mg Tegretol daily, was switched to generic carbamazepine and suffered a seizure that required hospitalization. Her seizures were controlled by intravenous diazepam. She was returned to Tegretol and has remained seizure-free for almost a year.

A 22 year old woman who had been seizure free on 800 mg Tegretol daily joined an HMO and had to switch to generic carbamazepine. After 4 seizures in 4 days, accompanied by a rash on her face, arms and hands, she was seen in a hospital emergency room and returned to Tegretol. Her rash has cleared and she has remained seizure-free for 6 months.

NOTE: Case reports were published in The Lancet (attached) as a letter to the editor.

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

The Lancet, June 20, 1987

GENERIC VERSUS BRANDED CARBAMAZEPINE

SIR,—A generic drug is defined as a compound with the same chemical structure and pharmacological properties as that in a proprietary brand, but costing less. US Food and Drug Administration guidelines on bioequivalence allow for some variation in different formulations, and this can be important clinically if there is a very sharp threshold for therapeutic efficacy. The area under the curve and maximum drug concentration have to be within 25% of the values for the reference parent compound in 75% of the patients tested in a crossover bioequivalence study.¹ For example, in a bioequivalence study of 200 mg branded carbamazepine (Tegretol) 75% of patients on generic carbamazepine would have to fall into a 150 to 250 mg dose equivalence window. We have seen breakthrough seizures in three patients who were well controlled on tegretol and were switched to a generic preparation.

A 51-year-old man who had had partial complex seizures since childhood had been clinically stable and seizure-free for 9 months on phenytoin 200 mg and tegretol 1200 mg daily. At one clinic visit he was given a new prescription which was filled with generic carbamazepine. Within 5 days he had generalised tonic-clonic and partial complex seizures. After six seizures in 3 weeks he was referred for neurological evaluation. His medication was altered to tegretol and he has remained seizure-free for 6 months.

A 46-year-old woman with a history of partial complex generalised tonic-clonic convulsions had been seizure-free for 3 months while on 1600 mg tegretol daily. After one routine clinic generic carbamazepine was dispensed. Some days later she had severe generalised tonic-clonic seizures and had to be taken to hospital by ambulance. Her seizures were controlled by intravenous diazepam. Back on tegretol she has been seizure-free for almost a year.

A 22-year-old woman with a history of partial seizures lost her job and health insurance cover because of her seizure disorder. She joined a health maintenance organisation and had to switch to generic carbamazepine. Before that she had been seizure-free on 800 mg tegretol daily for a year. After experiencing four generalised seizures in 4 days, accompanied by a rash on her face, arms, and hands, she was seen in the hospital emergency room. Back on tegretol her rash cleared and she has been seizure-free for 6 months.

A patient who is clinically stable on 1000 mg tegretol may, when switched to a generic product, be taking a preparation that is equivalent only to 900 mg or even 800 mg of tegretol.² This effective reduction in dosage is enough, in some cases, to cause breakthrough seizures. This is not to say that the generic medicine is ineffective: if patients take enough of the generic medication to attain the blood carbamazepine levels they had with tegretol their seizures would be controlled. However, for a saving in costs of 4 cents a tablet the patient runs the risk of losing his driving licence for a year or being

involved in a serious accident. Moreover, the cost of visits to the emergency room and investigations may more than offset the savings made by switching formulations. There are several generic brands, and no way of predicting which a patient will receive.

In disorders where small changes in drug levels may have serious consequences, switching from a branded to a generic product is not always advisable. Any switch to a generic anticonvulsant drug should be accompanied by monitoring of blood levels for the first month, during which the patient should not drive. Once bioequivalence has been confirmed, the same generic product should be used every time the prescription is filled.

We thank Dr Seddiken Chakraverty for his valuable suggestions.

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CASE REPORT #3 (1984) -- Tolazamide (rated AB*) (13 sources)
First marketed 1966

Fourteen women (mean age 59 yr) diagnosed as type II diabetics had been stabilized on Tolinase (Upjohn) when they were switched to generic tolazamide. On average, these 14 patients remained on the generic product for 12 weeks prior to resumption of Tolinase. During this 12 week period, all patients experienced a loss of clinical control, determined by laboratory parameters: fasting blood sugar increased 53% and glycosylated hemoglobin increased 44% (statistically significant increases). Upon resumption of Tolinase, these measurements decreased significantly (fasting blood sugar decreased 38%, and glycosylated hemoglobin decreased 22%).

NOTE: Information presented by Upjohn at the FDA Hearing (September 1986) and published in Diabetes Care (Jan-Feb 1987). Publication attached.

* AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

LETTERS AND COMMENTS

Decreased Clinical Control of Diabetes After Tolazamide Substitution

One of the most controversial issues in diabetes mellitus management is the role of euglycemia in preventing long-term diabetic vascular complications (1). However, diabetologists agree that tight blood glucose control minimizes the risk of acute complications and helps avoid intermediate complications. Oral hypoglycemic drugs have been used for many years to maintain euglycemia in type II diabetic patients whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Published studies continue to document the absence of bioequivalence of different preparations of pharmacologic agents when administered in identical doses (2-8). In 1984, generically manufactured tolazamide was approved for marketing by the FDA. Shortly thereafter, 14 type II diabetic patients at the Community Health Improvement Center in Decatur, Illinois, previously stabilized on Tolinase (Upjohn,

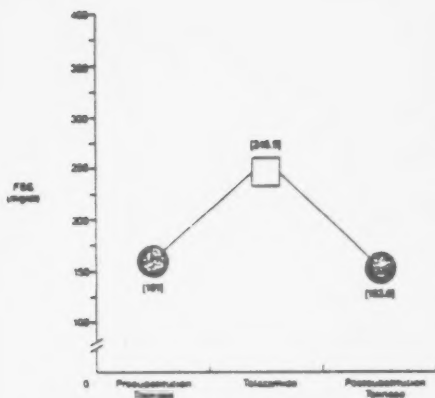


FIG. 1. Fasting blood sugar (FBS) levels during treatment with Tolinase (●) and generic tolazamide (□) in 14 patients.

Kalamazoo, MI), were switched to generic tolazamide. All experienced a loss of clinical control when switched to the generic product. Determination of loss of control was based on laboratory parameters, which included fasting blood sugar (FBS) and glycosylated hemoglobin (HbA_{1c}). Clinical con-

trol was reestablished when therapy with Tolinase was resumed. The dose of Tolinase or generic tolazamide, patients' weight, concurrent medications, and other relevant factors remained constant during the evaluation. The only apparent variable factor was the brand of tolazamide.

This account suggests an absence of bioequivalence between Tolinase and generic tolazamide. It does not represent a controlled prospective clinical study, but rather a retrospective series of cases in which loss of clinical control has been attributed to generic substitution. All the patients were women (8 Caucasian, 6 Black), mean age was 59 yr (range 38–78 yr), and mean duration of diabetes before generic substitution was 3.2 yr (range 6 mo to 15 yr). Mean duration on generic tolazamide after substitution and before resumption of Tolinase was 12 wk (range 4–17 wk).

Substitution of generic tolazamide for Tolinase resulted in a mean increase in FBS of 53% (161 to 245.9 mg/dl) and a mean increase in HbA_{1c} of 44% (9.84 to 14.20%) for all 14 patients. These increases were statistically significant ($P < .005$ and $P < .001$, respectively). Resumption of Tolinase resulted in a mean decrease in FBS of 38% (245.9 to 153.6 mg/dl) and a mean decrease in HbA_{1c} of 22% (14.20 to 11.07%) for all 14 patients. These decreases are also statistically significant ($P < .001$) (Figs. 1 and 2).

These data suggest that the two products are not equivalent in their capacity to stabilize diabetic patients, and substitution of generic tolazamide for Tolinase should not be performed or should be performed only under conditions in which the patient's response can be carefully monitored.

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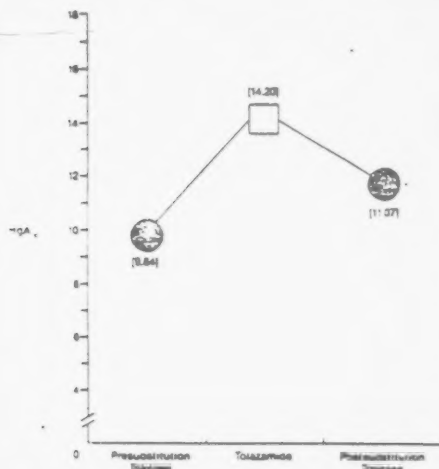


FIG. 2. Glycosylated hemoglobin (HbA_{1c}) levels during treatment with Tolinase (●) and generic tolazamide (□) in 14 patients.

**CASE REPORT #4 (1987) -- Valproic acid (rated AB*); 3 sources;
First marketed 1978**

A 19 year old female college student who had experienced complex partial and/or generalized seizures since the age of 11 had been seizure-free for 3 years while on Depakene (valproic acid) and Tegretol (carbamazepine). Scheduled office visits indicated that plasma levels for both valproic acid and carbamazepine were consistently within the recommended therapeutic range (valproic acid: 53-79 mcg/ml; carbamazepine: 6-8 mcg/ml). Her first seizure in three years (January 1987) occurred while driving home from school, resulting in her car leaving the highway and striking a street sign. Three days earlier the HMO dispensing her prescription had substituted generic valproic acid for Depakene (no change in the source of carbamazepine occurred). Since her return to Depakene, she has remained seizure-free.

NOTE: Attached is PMA Medical Report Form signed by attending physician and PMA investigator. Case report by attending physician accepted for publication in Neurology (manuscript attached).

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

PMA MEDICAL REPORT FORM

10.

REACTION INFORMATION				
Patient I.D. (in Confidence)	Age/DOB	Sex	Date of Reaction Onset	Check As Appropriate
N.K.	19yr	F	Jan 1987	☐ Patient Died ☐ Reaction Treated with Rx Drug ☐ In Patient Hospitalization ☐ Resulted in Permanent Disability ☒ Other <u>Convulsion</u>
Describe Reaction(s) and Treatment: 19yr old epileptic in excellent control x 3yrs, experienced seizure while driving car, 3 days after HMO substituted generic valproate for depakene.				
Reported to FDA: (Copies attached if available)		Reported to Manufacturer: (Copies attached if available)		
Contact: <u>No</u>		Contact: <u>Representative</u>		
Date:		Date: <u>March 1987</u>		
Further Correspondence:		Further Correspondence: <u>Manufacturer to be as</u>		
SUSPECT DRUG(S) INFORMATION				
Trade Name:	<u>Depakene</u>	Manufacturer:	<u>Abbott</u>	Lot #: <u>N/A</u>
Generic Name:	<u>valproic acid</u>	Manufacturer:	<u>N/A</u>	Lot #: <u>N/A</u>
Diagnosis:	<u>Partial complex seizures - Tonic-clonic seizures</u>			
Date of Substitution:	<u>Jan 1987</u>	Date First Diagnosed: <u>age 11</u>		
		Did reaction abate after stopping substituted product?		
		☒ Yes ☐ No Case: <u>one day post generic to Dk</u>		
CONCOMITANT DRUGS AND HISTORY				
Drug	Dose	Frequency	Route	Start Date
<u>Tegretol</u>	<u>N/A</u>	<u>N/A</u>	<u>PO</u>	<u>N/A</u>
				Stop Date
				<u>N/A</u>
Other Relevant History:				
Diagnosis		Date of Diagnosis		
<u>Epilepsy, partial-complex</u>		<u>onset age 11 yrs</u>		
SOURCE OF INFORMATION				
Name/Address/Phone		Signature		
JOHN MacDONALD, M.D.		<u>John T. MacDonald, MD</u>		
4225 Golden Valley Road		Date: <u>5/19/87</u>		
Minneapolis, MI. 55422		Investigator: <u>R.M. Howard</u>		
612 - 588 - 0661		Date: <u>8/19/87</u>		
Copy Left With Investigator: ☐ Yes ☒ No		Date: <u>8/20/87</u>		
COMMENTS AND ADDITIONAL INFORMATION				
<u>Follow-up fails to demonstrate any further seizures.</u>				

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Manuscript of Case Report by Dr. MacDonald
Accepted for Publication in Neurology

ABSTRACT

A 19 year old epileptic, seizure free for three years on valproate and carbamazepine experienced a generalized tonic-clonic seizure three days after substitution of her Depakene capsules (Abbott) with a generic form of valproic acid. In the absence of any other reasons for a breakthrough seizure, it is suggested that the abrupt change in commercial preparation of the valproate may have been responsible for this acute change in seizure control.

Valproic acid and its derivatives find extensive uses in the treatment of several types of seizures and in patients with multiple seizure types.¹ The drug in its various liquid and solid dosage forms is considered to be near completely absorbed.² This report documents an apparent breakthrough seizure in a young epileptic, seizure free for three years, after substitution of a generic brand of valproic acid to replace the Depakene capsules (Abbott) that the patient had been taking continuously for many years.

Case Report:

A 19 year old female college student had been seizure free for a period of three years after having been stabilized on an antiepileptic drug (AED) regimen comprised of valproic acid capsules (Depakene, Abbott) and carbamazepine (Tegretol, Geigy). She experienced her first seizure in three years, subsequently diagnosed as a tonic-clonic seizure, while driving home from school. During this episode, the car left the highway and struck a street sign but she escaped injury except for minor bruising. The patient indicated that no aura had preceded the seizure.

Upon questioning, the patient reported that three days earlier she had begun taking a generic form of valproic acid capsules that differed in appearance from Depakene. She had been given the generic product because of an Health Maintenance Organization (HMO) requirement that mandated that pharmacists substitute generic products, where available, for those drugs that are listed in the HMO's formulary. Subsequent consultation with the pharmacist confirmed that a generic product had been dispensed to the

patient in place of Depakene Capsules. No other change had been made in the medication regimen or in the source of the carbamazepine product.

The patient's medical history from age eleven indicated she had experienced 4-5 complex partial and/or generalized seizures per year. Phenytoin and ethosuximide were unsuccessful in controlling these seizures. At age 16, seizure control finally was achieved with valproic acid capsules and carbamazepine tablets. The patient remained on this AED regimen for the next three years, during which time frequent therapeutic drug levels were obtained. Plasma trough concentrations of both drugs (valproate 53-79 mcg/ml and carbamazepine 6-8 mcg/ml) were consistently within the recommended therapeutic range. The patient's medical status was evaluated every three months at regularly scheduled office visits.

This patient's compliance with drug therapy has been excellent. Except for the use of over-the-counter ibuprofen for dysmenorrhea, she takes no other medication and does not use alcohol. There is no history of drug abuse.

Within one day following the seizure, she resumed taking Depakene Capsules. Plasma valproic acid and carbamazepine levels obtained two weeks later were within the therapeutic range. Follow-up six months after the car accident has not demonstrated any further seizures.

DISCUSSION:

This case report highlights a possible cause of loss of seizure control that may be poorly recognized and reported. This previously well controlled epileptic's breakthrough seizure seemed most likely to have

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resulted from the abrupt substitution of a different commercial preparation of valproic acid, possibly resulting in a significant change in plasma AED levels. Unfortunately acute plasma AED levels were not available in this case. The combination of valproic acid and carbamazepine may produce complex drug interaction which might be affected by differences in the bioavailability of some of the commercial products now available.³

Since several generic anticonvulsant products are now available, physicians need to be aware that generic substitution may occur without their knowledge and this may possibly contribute to actual loss of seizure control in some patients.

REFERENCES

1. Penry JK. Epilepsy: Diagnosis, Management, Quality of life. New York: Raven Press. 1986:14-21.
2. Klotz U, Antoin K. Pharmacokinetics and bioavailability of sodium valproate. Clin. Pharmacology and Therapeutics 1977;21(6):736-743.
3. Reynolds EH, Shorvon SD. Monotherapy or polytherapy for epilepsy? Epilepsia 1981;22:1-10.

CASE REPORT #5 (1986) -- Propranolol (rated AB*); 18 sources;
First marketed 1968

A 67 year old male with a history of hypertension and heart disease since 1981 was on Inderal (propranolol) at 40 mg every 8 hours which controlled his blood pressure and angina. He remained clinically stable for 5 years at which time he was switched to generic propranolol. The patient noted no subjective changes other than an increase in chest pain. Upon a visit to his physician, however, an increase in blood pressure and an irregular heart beat were noted. After two months, Inderal was reinstated at the same dose and the patient's blood pressure and angina are in good control.

NOTE: Information provided through interview with the physician who testified at FDA Hearing noting problems with generic substitution. Attached are PMA investigator's Case Summary and PMA Medical Report Form signed by PMA investigator and attending physician.

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

PMA Investigator's Case Summary

Summary of case E.K. - Dr. Thomas A. O'Connor - Milwaukee, WI - July 29, 1987

This 67 year old male patient has a history of hypertension, heart disease and obesity since 1981. He was also diagnosed as a diabetic in July 1986.

When placed on 20mg of Inderal three times a day in December 1981 his control was only fair. He was placed on 40 mg every 8 hours in February 1982 and was well controlled in that his blood pressure and angina were not a problem any longer. He remained in good control until January 1986. The patient was switched to generic propranolol in January 1986, but the patient noted no subjective change. When the patient visited his doctor on March 4, 1986 the doctor noted an increase in blood pressure to 150/70 and an irregular heart beat. The patient reported an increase in chest pain. In May 1986 propranolol was discontinued and Inderal was restarted. The patient continues on Inderal at the time of this report, and the patient is in good control.

PMA MEDICAL REPORT FORM

19.

REACTION INFORMATION

Patient I.D. (in Confidence) E. K.	Age/DOB 11/10/18	Sex M	Date of Reaction Onset 3/4/86	Check As Appropriate
Describe Reaction(s) and Treatment: Change in heart beat - EKG 3/4/86 multiple Pk BP ↑ 130/80 → 150/70 Returned to baseline				☐ Patient Died ☐ Reaction Treated with Rx Drug ☐ In Patient Hospitalization ☐ Resulted in Permanent Disability ☒ Other: Returned to baseline
Reported to FDA: (Copies attached if available)		Reported to Manufacturer: (Copies attached if available)		
Contact: N/A. sent on 1639		Contact: Not necessary		
Date: 3/17/87		Date:		
Further Correspondence: None		Further Correspondence:		

SUSPECT DRUG(S) INFORMATION

Trade Name: Lideral	Manufacturer: aerost	Lot #: N/A
Generic Name: Propoxyphene	Manufacturer: Lederle	Lot #: N/A
Diagnosis: Hypertension, Heart Disease, Diabetes, Obesity		
Date of Substitution: 1/86	Did reaction arise after stopping suspicious product? ☒ Yes ☐ No Date: 5/86	

CONCOMITANT DRUGS AND HISTORY

Drug	Dose	Frequency	Route	Start Date	Stop Date
Lidoprin	0.25mg	QD	PO	2/9/82	Still on
Diazide	1 tab	QD	PO	12/7/81	Still on
Diazeta	5mg	QD	PO	7/86	7/86 still on
Diazeta	10mg	bid	PO	1/87	Still on

Other Relevant History:

Halter Monitor change
increased angina

Date of Diagnosis:

3/86
3/86

SOURCE OF INFORMATION

Name/Address/Phone THOMAS A. O'Connor, M.D., S.C. 1363 North Prospect Avenue Milwaukee, WI 53202 414 - 481 - 7020	Signature: T. A. O'Connor Date: 7/29/87
	Investigator: P. M. Howard Date: 7/29/87
Copy Left With Investigator: ☐ Yes ☒ No	

COMMENTS AND ADDITIONAL INFORMATION

Patient did not note the changes. Dr. O'Connor noticed the changes on examination. Patient complained of chest pain

CASE REPORT #6 (1983) -- Chlorpropamide (rated AB*); 12 sources;
First marketed 1958

A 56 year old woman who was diagnosed as a diabetic in 1982 had been clinically stable for almost a year while treated with 100-150 mg Diabinese (chlorpropamide). Her pharmacist substituted generic chlorpropamide in July 1983. By October, her blood sugar had risen from ~150 to 376, and she had developed multiple infections which did not respond to medications. By December, she was in very poor health with rising blood pressure and severe ankle edema, continuing weight loss and chest pains. At this time she was hospitalized and placed on 350 mg of Diabinese. Her blood sugars returned to ~150 and she has remained in control on Diabinese.

NOTE: Information provided through interview with attending physician. Attached are PMA investigator's Case Summary and PMA Medical Report Form signed by attending physician and PMA investigator.

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

PMA Investigator's Case Summary

John Campbell, M.D.
Patient: J.C.

9/1/87

This 56 year old female diabetic had been in good control for about a year while taking 100-150 mg. Diabinese per day. Her blood sugars ranged in the mid 100 level. Sometime in July of 1983 the patient was changed to generic chlorpropamide by her pharmacist. On 10/10/83 her blood sugar was 376. In September of 1983 she developed multiple infections. Her flu-like symptoms did not respond to medication and she developed ear infections which were difficult to treat. By December of 1983 she was in very poor health. Her blood pressure was on a continual rise and she developed severe ankle edema, a continuing drop in weight and chest pains. She was hospitalized in December 1983 at which time she was placed on Pfizer's Diabinese. She is still on 350mg of Diabinese a day and she is in very good control.

PMA MEDICAL REPORT FORM

REACTION INFORMATION				
Patient ID. (in Confidence) <i>J-C1</i>	Age/DOB <i>6/5/27 F.</i>	Sex <i>F.</i>	Date of Reaction Onset <i>10/10/83</i>	Check As Appropriate
Describe Reaction(s) and Treatment: <i>Complete loss of control of Diabetes Hospitalized 12/83 - Very ill - injection, increased blood pressure, severe weight loss.</i>				☐ Patient Died ☒ Reaction Treated with Rx Drug ☒ Patient Hospitalization ☐ Resulted in Permanent Disability ☒ Other Change of Drug
Reported to FDA: (Copies attached if available)		Reported to Manufacturer: (Copies attached if available)		
Contact: Date: Further Correspondence:		Contact: Date: Further Correspondence:		
SUSPECT DRUG(S) INFORMATION				
Trade Name: <i>Glipizide</i>		Manufacturer: <i>Pfizer</i>	Lot #: <i>N/A</i>	
Generic Name: <i>Chlorpropamide</i>		Manufacturer: <i>W.F. Hoffmann</i>	Lot #: <i>N/A</i>	
Diagnosis: <i>Diabetes</i>		Date First Diagnosed: <i>10/29/82</i>		
Date of Substitution: <i>July 1983</i>		Did reaction abate after stopping substituted product? ☒ Yes ☐ No Date: <i>12/83 (Hospital)</i>		
CONCOMITANT DRUGS AND HISTORY				
<i>Diagide</i>	Dose <i>3-6 x per week</i>	Frequency	Route <i>PO</i>	Start Date <i>long standing till on</i>
Other Relevant History: <i>Flu like infection & Ear infection 9/28/83</i>				
Diagnosis <i>Ch. Colon (reaction)</i>		Date of Diagnosis <i>1977</i>		
<i>Hysterectomy</i>		<i>1977+</i>		
<i>Mild Hypertension</i>		<i>150/90 10/29/82 (Loss of wt.)</i>		
SOURCE OF INFORMATION				
Name/Address/Phone <i>John W. Campbell, M.D. 104 Carolina Avenue Brookneal, Virginia 24528 804 - 376 - 2325</i>		Signature: <i>John W. Campbell</i> Date: <i>9/1/87</i>		
		Investigator: <i>Robert M. Howard</i> Date: <i>9/1/87</i>		
Copy Left With Investigator: ☒ Yes ☐ No				
COMMENTS AND ADDITIONAL INFORMATION				

Trade-Name

Drug	Genetic=Q	Dose	Frequency	Total Daily Use	Route	Start Date	Stop Date	Response (Therapeutic vs. other)
Diabinese	T	100mg	OP	100mg	PO	10/29/82	11/8/82	Good control
"	T	100mg	1 1/2 tabs	150mg	PO	11/9/82	5/19/83	100mg
Chlorpropamide	G	100mg	bid	200mg	PO	7/8/83	10/10/83	Out of control
"	G	100mg	tid	300mg	PO	10/10/83	11/7/83	"
"	G	250	1 qd	250mg	PO	11/8/83	11/14/83	"
"	G	250	1 qd	450mg	PO	11/15/83	11/21/83	"
"	G	250	bid	500mg	PO	11/22/83	1/25/84	Diabinese - okay, but
Diabinese	T	250	1 qd	350mg	PO	12/1/83	5/20/84	Good control

RELEVANT TESTS/LABORATORY DATA

Test Discard Results
Sugars, Date Blood Sugar

Date	Test Discard Results	Sugars	Date	Blood Sugar
10/29/82	346	1/25/85	254	
11/8/82	175	6/28/85	147	
11/19/82	112	9/25/85	159	
5/7/83	169			
10/10/83	376			
10/19/83	301			
11/11/83	304			
11/7/83	304			
11/14/83	374			
11/21/83	226			

CASE REPORT #7 (1981-1982): Furosemide (rated AB*) (15 sources)
First marketed 1966

Hoechst Roussel (manufacturer of Lasix) received reports on more than 75 patients reported to have experienced treatment failures when switched from Lasix to a generic furosemide). Nine of these cases are documented (no other precipitating factor was considered present):

1. 79 year old female treated for congestive heart failure (CHF) with Lasix; dose titration required to stabilize over a 3 week period. She was switched to generic furosemide and within 2 days was admitted to the hospital with shortness of breath, less frequent urination, diuresis, rales, and rhonchi. Returned to Lasix and restabilized.
2. 76 year old male with CHF controlled with Lasix for 8 months when switched to generic furosemide. Within 2-3 weeks, patient complained of orthopnea, pretibial edema, rales, and S3 heart sound. Returned to Lasix and restabilized within 4 days.
3. 80 year old female treated with Lasix during hospital stay and stabilized. Upon release, her prescription was filled with generic furosemide during which time 6 visits to the physician were required for increasing dyspnea and swelling of the legs. Rehospitalization was required; Lasix was resumed and control was resumed within 4 days.
4. 82 year old female stabilized for 4 years on Lasix for CHF. 5 months following a switch to generic furosemide, she was admitted to the hospital due to increasing chest pain, weakness, shortness of breath and sweating. Lasix resumed and restabilized within 4 days.
5. 72 year old female stabilized on Lasix during hospitalization following a small MI. Upon release, her prescription was filled with generic furosemide and within two months was in mild CHF. Lasix resumed and restabilized.
6. 57 year old female stabilized for several years with Lasix for CHF. Within two weeks of substitution of generic furosemide, she developed rales and was hospitalized. Lasix resumed and restabilized.
7. Female with chronic renal edema treated for 15 years with Lasix. Soon after receiving generic furosemide, she developed increased edema. Lasix resumed and restabilized.
8. 93 year old male treated with Lasix for CHF. Generic furosemide substituted and over the next 10 weeks, he suffered increased edema, increased blood pressure and weight gain. Lasix resumed and restabilized.

9. 91 year old female treated with Lasix for CHF. Generic furosemide substituted and over 2 months, she suffered from weight gain, increased blood pressure, and lung congestion. Lasix resumed and restabilized.

NOTE: Information provided by Hoechst Roussel (attached).

* AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

Hoechst-Roussel Pharmaceuticals Inc.

Routes 202-208 Hards • Somerville, New Jersey 08876
Telex 833-648 • Cable Hoechstus, Somerville, N.J.

Hoechst 

Bioequivalency studies required by FDA allow variations in bioavailability of $\pm 30\%$ among phenothiazine products, and $\pm 20\%$ between brands of furosemide. These variations could cause unanticipated clinical problems when elderly patients stabilized on the innovator brand are switched to a generic.

There are now several manufacturers approved by FDA to make generic furosemide tablets. These furosemide tablets appeared in the marketplace beginning August, 1981. To date, we have knowledge of and collected data on more than 75 patients reported to have experienced a treatment failure when they were switched from LASIX to one of the generic furosemides. Most of these reports involved patients being treated for congestive heart failure (CHF) who became decompensated on the generic product. Some of these reports were not well documented, and, in others, the failure could possibly be attributed to lack of compliance or deterioration of clinical condition. Enclosed are summaries of nine clear-cut cases which were documented to have deteriorated while on the generic and returned to their previous state of control once the LASIX brand of furosemide was reinstated. These cases seem to be straight forward.

TREATMENT FAILURES WITH GENERIC FUROSEMIDE**9 CASE SUMMARIES**

Furosemide Case 1

CASE: GF1

AGE: 79

SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: S/P Hysterectomy
S/P Myocardial infarction
S/P Mastectomy
S/P Pulmonary edema
Long-standing paroxysmal atrial fibrillation

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	100 mg	12/30/81-1/11/82
Lasix® (furosemide)	120 mg	1/12/82-1/18/82
Lasix® (furosemide)	140 mg	1/19/82-1/26/82
Generic furosemide	140 mg	1/26/82-1/28/82
Lasix® (furosemide)	140 mg	1/29/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This elderly woman had been treated for congestive heart failure for two years when she was first admitted to the care of the reporting physician. After several adjustments to her Lasix® dosage, her CHF appeared stable and controlled until her Lasix® tablets prescription was refilled with a generic furosemide. Within two days she went to the ER because of shortness of breath and because she noted that she was not urinating as frequently. She took Lasix® just before visiting the ER and the characteristic diuresis had begun. On physical examination she had rales and rhonchi. Chest X-ray revealed increasing failure and she was admitted.

By the second hospital day, her lungs had cleared. She was discharged in a few days and continued on her previous dose of Lasix®.

The reporting physician could find no other precipitating factor for decompensation in this patient.

Furosemide Case 2

29.

CASE: GP2

AGE: 76

SEX: Male

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: Hypertension
Atrial fibrillation

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	80 mg	4/81-11/01/81
Lasix® (furosemide)	160 mg	11/02/81- 1/03/82
Generic furosemide	160 mg	1/04/82- 1/18/82
Lasix® (furosemide)	160 mg	1/19/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This elderly man was treated with Lasix® tablets and his congestive heart failure was controlled when a generic furosemide product was substituted. Within 2-3 weeks the patient complained of orthopnea. On physician examination the patient had pretibial edema, rales and an S3 heart sound. His weight had increased 2.7 kg. The physician prescribed Lasix® brand furosemide at the same dosage and symptoms resolved within four days. The patient was continued on Lasix®.

The reporting physician found no other precipitating factor for decompensation in this patient.

Furosemide Case 3

CASE: GP4

AGE: 80

SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: Diabetes mellitus
 Atrial fibrillation
 Bronchitis
 Arteriosclerotic heart disease
 Cholelithiasis

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	40 mg	2/09/82-2/10/82
Lasix® (furosemide)	80 mg	2/11/82-2/17/82
Generic furosemide	80 mg	2/18/82-4/15/82
Generic furosemide	40 mg	4/16/82-5/05/82
Generic furosemide	80 mg	5/06/82-5/12/82
Lasix® (furosemide)	80 mg	5/12/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This 80-year-old woman was started and stabilized on Lasix® tablets during a hospital stay. Her prescription after discharge was filled with generic furosemide. During the three months following discharge, she was seen six times by her physician for increasing dyspnea and swelling of the legs. An intravenous injection of 20 mg Lasix® resulted in a half day's improvement.

After readmission to the hospital she was given 80 mg Lasix® po and diuresed three pounds by the next morning. In four days of hospital stay the patient lost seven pounds and was discharged with her symptoms much improved. The patient at last report remained controlled on Lasix® brand furosemide.

The reporting physician found no other precipitating factor for decompensation in this patient.

Furosemide Case 4

CASE: GF7

AGE: 82

SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES:

Hypertension
Coronary insufficiency
Diabetes mellitus
Angina pectoris
Arteriosclerotic heart disease
Degenerative joint disease

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	40 mg	1/78-12/11/81
Generic furosemide	40 mg	12/12/81- 5/03/82
Lasix® (furosemide)	40 mg	5/04/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This 82-year-old woman had used Lasix® tablets for 11 years, the last four years at 40 mg daily, with good control of her congestive heart failure. About five months after being dispensed generic furosemide she was admitted to the hospital because of increasing chest pain, weakness, shortness of breath and sweating. Three days before admission she was given Lasix® brand and noted a different appearing tablet and that she began urinating frequently. She commented that with the generic furosemide she did not have to worry about looking for a bathroom when she took her "water pill." She was discharged in four days on Lasix®.

No other predisposing factor for decompensation was found in this patient.

Furosemide Case 5

32.

CASE: GF11

AGE: 72

SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: S/P Myocardial infarctions x 2
S/P Triple bypass coronary artery surgery
S/P Mitral valve replacement

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	80 mg	Short time-3/82
Generic furosemide	80 mg	3/82-4/21/82
Lasix® (furosemide)	80 mg	4/22/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This 72-year-old woman with a long cardiac history was stabilized on Lasix® tablets 80 mg daily in the hospital following a small myocardial infarction. Upon discharge her prescription was filled with generic furosemide. About two months later she was in mild congestive heart failure, but the treating physician could find no precipitating factor. Upon discovery that a generic furosemide was being used, the physician ordered Lasix® brand (no dosage change) and the patient improved.

Furosemide Case 6

CASE: GF28 AGE: 57 SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: S/P Aortic and mitral valve replacements

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	80 mg	Years - 6/15/82
Generic furosemide	80 mg	6/16/82-6/29/82
Lasix® (furosemide)	80 mg	6/30/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This 57-year-old woman was treated for several years with Lasix® tablets 80 mg daily for congestive heart failure. Within two weeks of using generic furosemide she developed rales. She was hospitalized briefly, treated with intravenous Lasix® and restabilized on Lasix® tablets. No other precipitating cause for her decompensation could be found.

Furosemide Case 7

34.

CASE: GF32

AGE: Unknown

SEX: Female

INDICATION FOR FUROSEMIDE: Chronic renal edema

OTHER DIAGNOSES: Thyroid dysfunction

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	40 mg	15 years
Generic furosemide	40 mg	Several days
Lasix® (furosemide)	40 mg	Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This woman with chronic renal edema had been treated for fifteen years with Lasix® tablets. Soon after receiving generic furosemide, she reported to her physician that her furosemide was not working. She developed increased edema.

She was again treated with Lasix® brand and her edema was satisfactorily controlled.

Furosemide Case 8

CASE: GF35

AGE: 93

SEX: Male

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: Schizophrenia
Recurrent skin cancer
Ectropion
Cataracts

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	20 mg	? - 7/15/82
Generic furosemide	20 mg	7/15/82-10/02/82
Lasix® (furosemide)	20 mg	10/03/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This elderly nursing home resident was treated with Lasix® tablets to control his congestive heart failure. Generic furosemide was substituted and over the next 10 weeks he had increased edema, increased blood pressure and weight gain. Lasix® brand was again used and control was regained.

Furosemide Case 9

36.

CASE: GF36

AGE: 91

SEX: Female

INDICATION FOR FUROSEMIDE: Congestive heart failure

OTHER DIAGNOSES: Arthritis
Mild renal failure

FUROSEMIDE TREATMENT:

<u>Drug</u>	<u>Total Daily Dose</u>	<u>Duration/Dates</u>
Lasix® (furosemide)	80 mg	7 - 8/82
Generic furosemide	80 mg	8/82 - 10/15/82
Lasix® (furosemide)	80 mg	10/16/82-Continued

DESCRIPTION OF TREATMENT FAILURE, ITS TREATMENT AND OUTCOME:

This nursing home resident was treated with Lasix® tablets 80 mg daily for a lengthy but unknown period to control congestive heart failure. During two months' treatment with generic furosemide she had weight gain, increased blood pressure and lung congestion. These cleared after Lasix® brand was again used.

CASE REPORT #8 (1987) -- Methylphenidate (rated AA*); 2 sources;
First marketed 1956

A 9 year old male with a long history of hyperactivity with DSMIII diagnosis of ADDH, had been successfully treated and controlled for 2 years with a daily dose of 20 mg of Ritalin (methylphenidate). The HMO substituted generic methylphenidate in April 1987 and within one day, the school reported resumption of the patient's hyperactivity which persisted for one week. Ritalin was reinstated at the same dose and with 24 hours, the school reported markedly improved behavior. The patient remains in excellent control.

NOTE: Information provided through interview with the physician reporting the problem with valproic acid substitution. Attached is PMA Medical Report Form signed by attending physician and PMA investigator.

*AA: Products that are not regarded as presenting either actual or potential bioequivalence problems.

PMA MEDICAL REPORT FORM

38.

REACTION INFORMATION				
Patient L.D. (in Confidence)	Age/DOB	Sex	Date of Reaction Onset	Check As Appropriate
D. S.	9YR	M	April 1987	
Describe Reaction(s) and Treatment:				☐ Patient Died ☐ Reaction Treated with Rx Drug ☐ In Patient Hospitalization ☐ Resulted in Permanent Disability ☒ Other Poor clinical effective
9Y old male with long history hyperactivity with DSM-III diagnosis of ADDH, treated successfully for 2 years with Ritalin 16mg b.i.d. HMO substituted generic methylphenidate and school reported hyperactivity returning within next day, persisting for one wk, then mother bought Ritalin and within 24 hrs, school reported behavior was again markedly improved.				
Reported to FDA: (Copies attached if available)		Reported to Manufacturer: (Copies attached if available)		
Contact:	NO	Contact:	NO	
Date:		Date:		
Further Correspondence:		Further Correspondence:		
SUBJECT DRUG(S) INFORMATION				
Trade Name:	Ritalin	Manufacturer:	Lot #: N/A	
Generic Name:	Methylphenidate HCl	Manufacturer:	Lot #: N/A	
Diagnosis:	ADDH	Date First Diagnosed:	1985	
Date of Substitution:	April 1987	Did reaction arise after stopping substitute product? ☒ Yes ☐ No Date: 24 April 1987 for Ritalin		
CONCOMITANT DRUGS AND HISTORY				
Drug	Dose	Frequency	Route	Start Date
None				
Other Relevant History:				
Diagnosis		Date of Diagnosis		
None				
SOURCE OF INFORMATION				
Name/Address/Phone	Signature			
John T. MacDonald MD	John T. MacDonald MD			
1612-5580661	Date: 3/19/87			
4225 Golden Valley Rd	Investigator: R.M. Howard			
MPIS, NW 55422	Date: 3/20/87			
Copy Left With Investigator: ☐ Yes ☒ No				
COMMENTS AND ADDITIONAL INFORMATION				

CASE REPORT #9 (1987)

Antiepileptic drugs (e.g.):

Carbamazepine (rated AB*); 5 sources; First marketed 1968
Phenytoin (rated AB* for extended; BX for prompt); 3 sources
extended, 4 sources prompt; First marketed pre-1938
Valproic acid (rated AB*); 3 sources; First marketed 1978

The Epilepsy Institute issued a cautionary alert to physicians and consumers about switching to generic anticonvulsants after having reviewed information on an increasing number of reports of breakthrough seizures after such a switch. Individual documentation has not been made available about the specific cases. At least 16 cases are reported of breakthrough seizures with another 48 complaints of problems as a result of switching.

NOTE: Information reported in the New York Journal of Epilepsy
(attached)

*AB: Drug products that are considered to be therapeutically equivalent to other pharmaceutically equivalent products and which meet the necessary bioequivalence requirements.

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SWITCHING TO GENERIC MEDICATIONS LINKED TO RENEWED SEIZURE ACTIVITY

A physician and consumer cautionary alert has been issued by the Epilepsy Institute after receiving and confirming reports linking generic anticonvulsants with renewed seizure activity in previously seizure free epileptic patients who were switched from brand name pharmaceuticals to generics.

"It appears that equivalent doses of generic anticonvulsants are not necessarily absorbed or excreted at the same rate as the brand name products; therefore, proactive blood levels may not be sustained. The result can be the sudden and totally unsuspected renewal of seizure activity in people with epilepsy who have been seizure free for years under a regimen of brand name anticonvulsant medications," stated Dr. Hart delC. Peterson, Past Chairman of the Epilepsy Institute's Professional Advisory Board and Professor of Neurology and Pediatrics at New York Hospital-Cornell Medical Center.

Dr. Peterson also pointed out that there appear to be differences between generic products produced by different manufacturers. This means that switching from a known effective generic or brand-name anticonvulsant to an alternative generic product may result in loss of previous seizure control.

Dr. Louis Laxagna, Dean of the Sackler School of Graduate Biomedical Sciences at Tufts University, furthermore asserted in USA Today that "the FDA does not require that generics undergo the same tests to prove efficacy that brand-name medicines must undergo in order to get approved." In fact, as Dr. Larry L. Schwartz, President of Health Policy Interna-

Continued page 18 column 1

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found, observed in a letter to the N.Y. Times, "The Food and Drug Administration does not support the notion that generic products must be identical to the standard product. It frequently accepts as interchangeable products that differ from the standard with regard to their bioavailability by as much as 60 percent."

Dr. Thomas Brown, a Boston University School of Medicine neurologist at the Boston VA Hospital, agrees with these findings. As he explained in the Boston Globe, "the difference in absorption rates between generic and brand name anticonvulsants may be crucial, because too rapid absorption may produce toxic effects and too slow absorption may be inadequate to prevent a patient from seizures."

In an interview in "Medical World News," Dr. R. E. Leppik advised "If the patient's well-controlled, don't switch drugs." Dr. Leppik also stated that four of his well-controlled patients had seizures after switching from a brand-name to a generic. Dr. Leppik, associate consulting professor and director of research at the Univ. of Minnesota's comprehensive epilepsy program, went on to say that even if the stated purpose of a switch to generics is economic, "using a little on a drug isn't cost-effective if it leads to a \$75 or \$100 emergency room visit and possible hospital admission."

In regard to cost, a recent article in the journal of the American Medical Association concluded "...the consumer is best advised to search for low prices without regard to whether the drug is brand or generic. The wide variance in price means that search, with its own cost, will usually be beneficial, but that there can be no guarantee of finding the lowest price. Nor can there be any guarantee that either the generic or brand drug will always carry the lowest price. In short, while a rule of 'always buy generic' will save the consumer money, a rule of 'always seek and buy the least expensive, whether generic or brand' will save even more money." In the same issue of the journal, Dr. Langan noted that "for some drugs the difference in mean price is trivially small, and it is not unusual for a generic drug to cost more than a brand name drug."

Dr. Alan Kerkman, a preventative medicine specialist who hosts radio and TV talk shows as Boston, informed the Epilepsy Institute that his on-air discussion of brand name and generic drugs drew nearly 60 phone calls and letters from people who reported having problems after a prescription change, including calls from at least a dozen people who reported having seizures after switching to a generic anticonvulsant.

In view of the increasing number of reports of break-through seizures after a switch to a generic anticonvulsant, the Epilepsy Institute reviewed all available information, and issued a cautionary alert to physicians and consumers. Epilepsy Institute President, Ira L. Brady,

emphasized that the Epilepsy Institute was not questioning the efficacy of generic anticonvulsants when introduced and utilized as initial therapy in the newly diagnosed patient with epilepsy. The potential problem comes with switching from a brand name anticonvulsant to a generic, or from one generic manufacturer to another.

*There appear to be differences between generic products produced by different manufacturers. This means that switching from a known effective generic or brand-name anticonvulsant to an alternative generic product may result in loss of previous seizure control.**

Taking into account these and other medical findings, the Epilepsy Institute recommends that individuals who are on an effective regimen of brand name products continue to stay with those products, as the effects of a totally unexpected seizure can be disastrous.

*Brown, B.E. When, O.K. Pres. N.Y. Cost and Price of Carboxamide Based and General Pharmaceuticals, JADA 1984; 116:3715-3716.

*Continued from page 9

on orally but this usually causes sedation. Alternatively, a different antiepileptic medication can be given intravenously until the patient is stabilized and carbamazepine can be administered orally.

A general principle of chronic drug therapy is to administer a medication at time intervals equal to the elimination half-life. The half-life of carbamazepine ranges from 5 to 24 hours after chronic treatment. However, the Tegeral brand of carbamazepine is slow to dissolve and behaves like a slow release formulation relative to most generic preparations. This reduces the peak concentrations and allows some, though not all, patients to take only two daily doses. Three or more daily doses are usually needed by young children and by patients who are taking other antiepileptic drugs.

Carbamazepine dosage requirements are also influenced by other factors including age, other diseases and pregnancy. Children and women in the last trimester of pregnancy, like patients

42, taking additional antiepileptic drugs, need relatively larger doses. For example, the average daily dose in children is 20 mg/kg, whereas the average adult dose is 10 mg/kg (800 mg).

Among patients who respond, most do best when carbamazepine blood levels are between 4 and 12 ug/ml. This therapeutic range is a good reference point for evaluating therapy, but at any time clinical issues are the most important determinants of therapeutic decisions. When levels are below 8 ug/ml side effects are rare; above 12 ug/ml they are increasingly common. Some patients tolerate higher levels, especially if they are taking only carbamazepine (monotherapy).

The most frequent side effects of carbamazepine include rash, dizziness, drowsiness, and diplopia (double vision). Gastrointestinal complaints are rare. Allergic reactions are an indication for stopping the drug. Rare, idiosyncratic side effects include worsening of idiopathic seizures in children with severe epilepsy of the Lennox-Gastaut type, hepatotoxicity, salt depletion, behavioral reactions, and movement disorders including rics. Neurological side effects due to high levels include drowsiness, vertigo, double vision, and incontinence. However, at therapeutic levels the lack of side effects involving mastication, mood, and behavior is an advantage of this drug relative to most other antiepileptics. Among those patients who need high levels to prevent seizures—patients in whom carbamazepine has a narrow therapeutic index, intermittent side effects can be caused by transiently elevated blood levels (high peaks). When this occurs, first make certain that the patient is taking the most slowly absorbed preparation. The alternative is to administer smaller, more frequent doses.

Severe hematological toxicity induced by carbamazepine such as aplastic anemia or agranulocytosis is very rare, currently estimated to occur about once per 10,000 patients. Thus the previous concerns about these potentially lethal adverse reactions have been assuaged by extensive experience in patients over the past two decades. However, mild, usually transient reductions in blood cell counts occur in approximately 15% of patients. This transient phenomenon almost never has clinical significance but should be monitored in case the blood cell counts falls below 1200 per mm³.

Because serious problems are so rare, there is no consensus about how frequently the blood count should be monitored during therapy with carbamazepine. I evaluate baseline blood counts before initiating carbamazepine, obtain follow-up counts four to six weeks later, and then every six months thereafter. If a marginally low count is obtained, more frequent counts are recommended.

From The Edward Mallinckrodt Department of Pediatrics and The Department of Neurology and Neurosurgery, SUNY at Stony Brook, Stony Brook University, St. Louis and The Division of Pediatric Neurology.

Mr. MOSSINGHOFF. In one drug-switching example cited in the appendix reported by a physician in the "Journal of the American Medical Association," already referred to in this hearing in connection with the testimony of Dr. Goyan, a 16-year-old girl who had been stable on the same antiepileptic medication for 9 years suffered a dramatic increase in her seizure frequency after being switched to a generic drug.

The physician stated in the JAMA article, and I quote, "In defense of the new regulations, the Food and Drug Administration, FDA, stated that it 'is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the agency as bioequivalent'." Continuing the physician's quote, "Our patient provides such a case."

PMA is particularly concerned about the indiscriminate switching of drug products, whether from generic to brand name or from one generic to another. Patients on maintenance regimes whose daily dosage must be individualized are especially at risk when drug products are changed.

Many such drugs are given to elderly patients and patients whose illnesses, such as heart failure or diabetes, can have life-threatening consequences if the treatment is inadequate.

Many maintenance drugs require dose titration because of factors such as inter-patient variability, the shape of the dose response curve, the therapeutic index of the drug, and the variable clinical course of the disease.

The case reports in the appendix to my statement demonstrate that patients with epilepsy, diabetes, cardiac disease, and hyperactivity experience problems following a switch from one version of a drug to another.

The Food and Drug Administration itself has acknowledged that of the 6,000 drugs listed in the Orange Book—formally known as Approved Drug Products with Therapeutic Equivalence Evaluations—about 20 percent have not been determined by the agency to be therapeutically equivalent to the pioneer products.

Many physicians and pharmacists are unaware that FDA assigns different therapeutic ratings to marketed products, and thus do not use this information in prescribing and dispensing.

This obviously raises a serious question as to why more than 1,000 drugs—that have neither been tested for safety and efficacy nor determined by the FDA to be bioequivalent to pioneer products that have been so tested—are allowed to remain on the market.

PMA believes that the process used by the FDA to approve generic drugs needs to be improved. Indeed, the FDA itself has stated that its testing procedures for approving generic drugs can be improved.

PMA believes that the FDA should (1) tighten the standards it uses to determine bioequivalence, by repudiating the across-the-board plus or minus 20 percent rule in favor of individualized drug-by-drug bioequivalence criteria.

Two, FDA should use existing FDA surveillance systems to collect and evaluate bioinequivalence data on generic products, and our specific recommendation in that regard is that the form used for adverse drug reactions—Form 1639—be specifically amended in both of its forms to add the manufacturer and the batch number.

As I understand it, that is done now for biological products, but not for drugs. We think that it would sharpen the FDA's surveillance if they were to add the manufacturer, since in many cases the doctor prescribes by brand name, but under substitution laws a different manufacturer's product is dispensed to the patient.

We think that there is an easy track there between the form that FDA uses and identifying the manufacturer and the lot number, whether that manufacturer be the brand name member of PMA or a generic-only company.

Senator METZENBAUM. Have you discussed that with the FDA?

Mr. MOSSINGHOFF. I believe Dr. Jennings has at some length.

Dr. JENNINGS. We have made that recommendation to the Food and Drug Administration.

Mr. MOSSINGHOFF. That was one specific recommendation that I believe we made during the October 1986 hearing that the FDA held on bioequivalence.

Third, we recommend that FDA extend the warning about the risk of switching drugs that they now use for drugs approved between 1938 and 1962 to all maintenance drugs approved through bioequivalence testing and include this caution in the product labeling until such testing is scientifically demonstrated to assure safety and effectiveness.

Finally, Mr. Chairman, in connection with issues of particular interest to the Subcommittee that I am pleased to appear before, competition within the research-based pharmaceutical industry is intense. Among PMA members, no company commands more than seven percent of total sales in the United States, and the top 20 companies combined have less than 75 percent of U.S. sales.

Through June 1987, 904 Abbreviated New Drug Applications, or ANDAs, have been approved for marketing since enactment of the Drug Price Competition and Patent Term Restoration Act of 1984.

The relatively new industry of companies that produce only generic drugs has captured an increasingly large share of the prescription drug market and is highly profitable. This new industry, far from suffering, is in fact thriving.

Mr. Chairman, this concludes the summary portion of my statement. I would appreciate that the remainder be placed in the record of this hearing.

Senator METZENBAUM. Your entire statement will be included in the record.

I want to say before I ask you any questions that the thrust of this hearing is not to question the contributions that have been made by the drug industry and that continually are made by the drug industry to our overall health concerns in this country.

I do not think there is anybody in the Congress or in America that does not appreciate the fact that the continued research that is being done by the pharmaceutical manufacturers is truly very important to the future health needs of the people of this country, and maybe the world as well.

So we are not in disagreement, and there is no effort to be anti-drug companies. The concern has to do with marketing practices, with attempts to denigrate the value of generic drugs, the reality of lower priced generic drugs being the equivalent of the name, market-brand drugs.

But that is our thrust, and I am sure that you and I understand each other on that particular point. But we certainly are not taking the pharmaceutical industry to task for not doing so much of that which has to be done in the area of research. We think they do it and we are glad that they do it.

Mr. MOSSINGHOFF. I appreciate that recognition, Mr. Chairman.

Senator METZENBAUM. Now, on page 13 of your written statement, you make a most serious charge. You contend that there are more than 1,000 drugs being marketed to the American people with the acquiescence of the FDA that have, quote, "neither been tested for safety or efficacy, nor determined by the FDA to be bioequivalent to those that have been so tested."

Now, what drugs are these, and can you tell me which drugs are you talking about, because I do not believe we can find any of those thousand drugs, nor do I think that the FDA confirms the accuracy of your statement? So I think we have to know which drugs you are speaking about.

Mr. MOSSINGHOFF. Mr. Chairman, these are the drugs that are listed in the Food and Drug Administration's so-called Orange Book that has been referred to by Professor Goyan previously.

These are the drugs which have a B rating, and it may be appropriate, John, if you have the Orange Book, to read what the FDA itself says about the B-rated drugs.

The drugs each have a letter rating in the Orange Book. Under B, on page 1-6, it says "Drug products that FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products."

So all of the drugs, and it numbers more than 1,000—perhaps Dr. Young can give a more precise number—it numbers more than 1,000 drugs listed in the Orange Book which are on the market in the United States that have never been tested for safety and efficacy under the new drug approval system that our companies use when they bring a pioneer drug out, nor have they been subjected to the ANDA bioequivalence testing that the FDA uses to determine the bioequivalence of generic drugs.

I do not think anyone disputes the fact that there are more than 1,000 drugs which have not been tested by FDA and is recognized as such by FDA. Now, the question we ask is, from a public health point of view: Why are those drugs even on the market? Why are they permitted to be marketed? I think that is a very legitimate question.

Senator METZENBAUM. We will have Dr. Young on later, but we found the statement that the FDA allowed 1,000 untested drugs on the market so shocking that we consulted a number of experts.

What we were told is that this list consists entirely of drugs that contain the same chemical ingredients as drugs that have been so tested. Now, is that your understanding of the facts?

Mr. MOSSINGHOFF. Yes, that is true, but they also suffer or may suffer from the problem that Professor Goyan mentioned. Let me refer, if I can, to Dr. Jennings.

Dr. JENNINGS. I think that is accurate, Mr. Chairman. These drugs are copies of the innovator's products and they are comparable in some sense to the drugs that are rated as A/B; that is, those that have been determined by FDA to be therapeutically equivalent.

lent to the innovator's product on the basis of bioequivalence testing in human subjects.

Those B-rated drugs that have not been so tested retain a B rating, and in some instances it is a rating B/X, which translates into insufficient data. So the drugs admittedly are copies of the innovator's product. They contain the same amount of the active drug, but they have not for one reason or another—

Senator METZENBAUM. Are you saying, Dr. Jennings, that the B-rated drugs are unsafe?

Dr. JENNINGS. I am saying we do not know.

Senator METZENBAUM. And the FDA has said in the book that they have not tested them, but that they have the equivalent components of those drugs that have been tested. Is that the thrust of what you are saying?

Dr. JENNINGS. That is essentially correct.

Senator METZENBAUM. Let me just go to the next question to you, Mr. Mossinghoff. How many of those 1,000 drugs are manufactured by PMA companies? Do you know?

Mr. MOSSINGHOFF. Mr. Chairman, I have not counted them. Several are. On those drugs, we are not charging that any are unsafe. We are saying that FDA itself indicates that it has not made the kind of determination that Congress required in 1984.

In 1984, Congress made a very conscious decision that chemical equivalence was not sufficient to bring a new generic on the market; the new generic had to be bioequivalent. These are drugs which have not been tested by FDA under that standard.

Senator METZENBAUM. Well, it is because of your testimony to that effect that we did—I think that Dr. Young saw fit to testify after your testimony and we will let him respond further on that subject.

But as I see it, I think there is no fear, there is no danger. They are the equivalent, but they have not been tested. Is that pretty much what you are saying, Dr. Jennings?

Dr. JENNINGS. I am saying they have not been tested. That is exactly right.

Senator METZENBAUM. As I understand your testimony, you suggest that substituting drugs within the bioequivalency range approved by the FDA can cause problems. Now, I have a number of questions about that.

First, let us clear about what we are talking about because I have noticed that the name-brand industry tends to mix terms and facts in a way that is very confusing to the consumer.

If the FDA approves a drug as a bioequivalent, generic substitute to a name brand, that drug is given an A rating. To get this rating, the generic manufacturer must prove that the drug is absorbed by the body within a range established by the FDA.

Now, this summer the Washington Post published a letter to the editor from you that warned of the dangers of substitution. You cited an example where you said a brand name had been substituted for a generic with adverse consequences to the patient.

My staff forwarded that letter to the FDA and asked for their comments. The FDA reply illustrates the shell game going on at the consumer's expense. According to the FDA, the two drugs involved in your example were two separate name drugs that are not

rated as bioequivalent by the FDA. In other words, they were separate drugs; they were not one generic and one brand name.

In fact, the FDA reported that it had specifically recommended to States and health care professionals that these products not be substituted because the FDA does not have evidence that the drugs are bioequivalent.

At the time you wrote the letter to the Post, were you aware of those facts?

Mr. MOSSINGHOFF. I was not aware, Mr. Chairman. Apparently, what you are saying is that was a B-type drug.

Senator METZENBAUM. That was a what?

Mr. MOSSINGHOFF. A B-type drug where the FDA had not—

Senator METZENBAUM. No. I think the point is they were two separate drugs. It is available from only two manufacturers, Eli Lilly and Sandoz, who are members of the Pharmaceutical Manufacturers Association. I believe them both to be separate drugs and that nobody claims that one is a substitute for the other.

I think there may have been some confusion in your fact situation when you wrote the letter to the editor.

Mr. MOSSINGHOFF. Well, let me say if there is, I would apologize to everyone for that. But I believe that the point that we were making—I wanted to make the point that PMA is not antigeranic. PMA as a representative of the brand name industry is not anti-generic.

We think there are problems that can be caused by switching from one version of a drug to another, as I said in my statement, whether from a brand name to a generic where there is close titration required or from a generic to a brand name.

I chose this for my article because I did not want to give only an example of where you go from a brand name to a generic-only manufacturer. What we say about switching we have recommended formally and officially in the submission that we made to the Food and Drug Administration. In that submission, it is our view that the across-the-board plus or minus 20 percent rule should be repudiated by FDA in favor of a drug-by-drug or category-by-category, tighter specification of what you need, and that they use advisory committees of practitioners in the field to help them make that specification.

The fact that you would switch from a generic-only manufacturer to one of the PMA companies producing a generic version of another pioneer drug is precisely what we are getting at.

We think that that could cause problems and we think FDA, one, should increase their surveillance and, two, should go a little more—

Senator METZENBAUM. What backup do you have, Mr. Mossinghoff, for your statement that switching from one drug to the other could cause problems? You are saying actually switching from a generic to a PMA-manufactured brand name product could cause problems, but what scientific backup do you have for that, since the FDA and what I would consider the overwhelming majority of scientific evidence indicates that where the drugs have been approved, where one just does not have the same brand name as the other or does not have the same generic name as the other, there indeed is a saving?

You are saying there should never be any switching and I just have to ask you what scientific backup do you have for that statement?

Mr. MOSSINGHOFF. Well, first let me say that I am not saying and PMA is not saying there should never be switching. We do say that switching, if it occurs, should occur with the knowledge of the physician who is attending the patient.

We think you really have to go back to the physician. In all of the political battles that we fight around the States, as well as the one that we were engaged in here on the amendment sponsored by Congressman Jacobs of Indiana over in the House on Medicare, the bottom line of the PMA position is that if a system permits mindless switching or required switching, it is not a good system. The physician should be involved in the switching.

Secondly, the FDA has chosen the plus-or-minus-20 rule to use for their determination.

Senator METZENBAUM. Does not that plus or minus 20 affect brand names as well as the generics?

Mr. MOSSINGHOFF. Absolutely.

Senator METZENBAUM. So that what you are saying is you have taken issue with that rule, but that does not really relate directly to the brand name versus the generics?

Mr. MOSSINGHOFF. Well, that is absolutely correct, and the fact is that the PMA companies' share of generics--and I define generics as all multisource products except the pioneer--is greater than half, as I think you indicated in your opening statement.

The best data I have is about 55 or 56 percent of all generics are produced by PMA companies, so we are not antigeneric. What we are saying is if there is a disease category--and epilepsy, I think, is one where most people recognize there is a problem--where the plus or minus 20 percent rule does not work well, we think FDA should back away from it, get the best advice they can, and perhaps write a tighter regulation.

That is our formal position, as I say, that we submitted to the FDA, and we will be interested to see what Dr. Young has to say about that.

Senator METZENBAUM. If the physician wants a particular brand name used, all the physician has to do is write the brand name on the prescription, so that makes it pretty simple.

Mr. MOSSINGHOFF. Well, in general, it is somewhat more complicated than that because in most of the States if the physician just writes the brand name on the prescription, there either is permissible switching or mandatory switching unless the physician writes another code, either "brand medically necessary," or "dispense as written, DAW," or if he signs on line one versus line two.

It is our position that the code that the physician uses should not be overly complicated, and that there should be an honest judgment on the part of the attending physician whether the brand name should be dispensed or whether a generic could be substituted. In no case should a drug be dispensed without the physician's knowledge.

Senator METZENBAUM. Well, you have said that you are not anti-generic, and yet I do not know whether you do not get hung on

your own words. The letter to the editor that you wrote is headed "The Danger of Generics." Now, that sounds pretty antigeneric.

Mr. MOSSINGHOFF. Well, Mr. Chairman, I think—

Senator METZENBAUM. You did not write the title?

Mr. MOSSINGHOFF. I was going to say we are all interested to see what headlines are put on the things we write, and that was not put on by me.

Senator METZENBAUM. But the fact is that was the interpretation that the letters to the editor—how he interpreted your letter, or she interpreted it. You start off saying, "We were disappointed to see the Post's editorial endorsing the gimmicky generic-prescribing scheme being considered by the House as part of the Medicare drug benefit."

Mr. MOSSINGHOFF. May I comment on that?

Senator METZENBAUM. Pardon?

Mr. MOSSINGHOFF. May I comment?

Senator METZENBAUM. Sure.

Mr. MOSSINGHOFF. First, I would say that I am not going to try to defend headline-writers. They are an interesting group.

Senator METZENBAUM. How about "gimmicky?"

Mr. MOSSINGHOFF. We think that the requirement that is in the House-passed Medicare bill which requires a physician to write the words "brand medically necessary" in his own handwriting is different from most of the States in the Union—and States, of course, regulate the practice of pharmacy—and that is gimmicky.

If the physician writes something different from that or he writes the initials, DAW, which throughout the profession means "dispense as written," the brand name will not be given. Even though the physician wants to do it and he writes the brand name in the prescription and he writes DAW, which is the code in most States, or he signs on the line that says "brand versus generic," it will be dispensed as a generic if he does not use the exact words.

Now, we are optimistic that maybe as that legislation progresses we will be able to defer to the States. We hope that we could defer to the States and let their existing laws on substitution apply and not have physicians have to learn two different laws, one for Medicare and one for everyone else.

But I say "gimmicky" is probably not a bad characterization. I will defend that, but I will not defend the headline.

Senator METZENBAUM. Let me ask you a question. Without referring to any particular company, do you think it appropriate that a company offer financial inducements to a physician to prescribe a brand name product rather than a generic product?

Forgetting what the inducement may be, does that not offend your sense of integrity and the physician's integrity?

Mr. MOSSINGHOFF. Let me say two things in response to that, Mr. Chairman. One is that PMA as an organization does not get involved in the marketing practices of our members, nor, I believe, under the antitrust laws could we get involved in specific marketing practices. So PMA does not address those issues, and I think our general counsel would get pretty nervous if we did.

Secondly, I do not think there ought to be financial inducements for a doctor to prescribe a brand name over a generic. I think the

doctor should provide the best care for his patient, and I think most doctors do.

Third, I would say that in the cases that I know where there are inducements given, normally they are to participate in some kind of a market survey or other information-gathering campaign, which I suspect the doctors probably would not have the time to do if there were not some kind of an inducement.

Now, I do not know in the specific case what the——

Senator METZENBAUM. I do not want to talk about specific members of your organization.

Mr. MOSSINGHOFF. In general, I can say that I do not personally think it is appropriate to offer financial inducements to doctors to prescribe whatever for their patients. I think they should act in the best interests of their patients.

Senator METZENBAUM. What would you think of putting on the agenda of the PMA the possibility of the PMA setting some ethical standards for the industry, because when we here in this meeting talk about a company and offerings about frequent flyers or whatever the name is that is used as an inducement, I do not think there is any question about it that those members of the media that are here, their articles do not single out, normally speaking, one or another company, but it becomes broad-brushed and it is an embarrassment to the industry?

I think it is a well-respected industry and I wonder whether or not the question of ethical sales tactics and techniques is not an appropriate one for the PMA's next board meeting.

Mr. MOSSINGHOFF. Can I take that under advisement and talk to our Executive Committee about it, and we will let you know?

Senator METZENBAUM. Would you let me know in writing, please?

Mr. MOSSINGHOFF. Yes.

Senator METZENBAUM. Now, you refer in your testimony to a recent story published in the Journal of the American Medical Association that discussed the failure with Primidone, the generic substitute for a name brand epileptic drug.

Has the PMA itself investigated this incident?

Mr. MOSSINGHOFF. I do not think we have. I think in this case we relied upon the report. It is case number one in the appendix to my statement, but let me ask Dr. Jennings to comment on that.

Dr. JENNINGS. No, sir.

Senator METZENBAUM. Do you know how many Primidone tablets have been taken by patients since the FDA-approved equivalent came on the market?

Dr. JENNINGS. I am sure there are very many.

Senator METZENBAUM. Over 400 million. Now, frankly speaking, you could have some change of medicine and you could have a result, but the result could have come about for a hundred different reasons and there is no pattern to look to except one case.

I must say that I am not a doctor, but I know enough about scientific research that one case does not a point make. You do not prove your point by saying, well, this happened in one instance, which is apparently what the JAMA article said.

According to the FDA, there have been 12 reports of drug failures involving the name brand product and only three involving a generic substitute. Are you aware of that?

Mr. MOSSINGHOFF. No, I was not aware of that. I would say that, again, in line with the earlier discussion, we could well imagine that if a patient is titrated in a critically important area, and, as I say, epilepsy is one that we are aware that the Epilepsy Institute and the Epilepsy Foundation are very concerned about generic substitution—we have seen physician alerts they have published.

Epilepsy seems to be an area where the plus- or minus-20 rule is not working very well. If a patient is titrated on a generic of a generic-only company, I think Dr. Jennings and his colleagues would caution against switching to a brand name on that one. So I do not know if that involves a brand name or not.

Senator METZENBAUM. You also refer to a study reported by a physician in a diabetes care journal that suggested problems when patients were switched from an Upjohn product to a generic.

As you noted, this was not a controlled study. However, an attempt was made to scientifically investigate the report by Upjohn. Are you aware that last year Upjohn reported to the Illinois Formulary Committee that Upjohn's investigation found no bioequivalency discrepancies between the two drugs?

In other words, the very company that could benefit from this report admitted the drugs in question were the equivalent of each other.

Mr. MOSSINGHOFF. No, I was not aware of that.

Dr. JENNINGS. I might comment on that. I think there are a few points here that have to be cleared up. We believe that there is a pattern of problems with the loss of control when patients are switched from one product to another, and this in spite of a determination by current methods that the drugs are bioequivalent.

In other words, what we are saying is that this system, good as it might be for many circumstances, apparently does not assure safety and efficacy under all expected conditions of use, and this is apparently showing up from time to time with patients who are on a maintenance regimen with drugs that must be titrated to the patient and where a switch occurs.

It is not surprising to me that the drugs involved in that study on a formal determination of bioequivalence satisfied FDA's requirements.

Senator METZENBAUM. You are actually saying that the matter of switching may be as risky in going from a generic to a brand name product as it is risky in going from a brand name to a generic?

Dr. JENNINGS. Exactly.

Senator METZENBAUM. PMA has made generic drugs an issue in lobbying on the catastrophic health care bill. One of the statements your ads made was that the program may not pay for the medicine your doctor wants to prescribe. I believe this is in quotes: "Instead, some bureaucrat in Washington will decide what medicines the Government will pay for."

Now, the drug provision passed by the House and that before the Senate both permit the doctor to specify that it is medically necessary that the prescription be filled with the brand specified.

Given that, what could you possibly have meant by your statement that medical decisions will be made by a bureaucrat?

Mr. MOSSINGHOFF. Mr. Chairman, that has nothing to do with generic versus brand. That has to do with whether or not the people who are managing the program will adopt a formulary under which the drug, whether it is generic or brand name, that is, the chemical requested, will not be dispensed or will not be reimbursed under the program.

That happens quite frequently in States in under-funded programs. The way you save money is to say we are simply not going to put an expensive patented drug, or its generic counterparts, on the formulary.

As an example, in the MediCal program in California—the State's Medicaid program—it took 26 months for the manufacturers of Tagomet, which was at that time recognized, as it is now, as a miracle antiulcer drug that obviates stomach surgery—it took 26 months for the company that manufactures that to get the officials in California to put it on the formulary.

The head of the Health Care Financing Administration, when he was testifying before the Ways and Means Committee in July, precisely said that if he has to implement this program and it is underfunded, the way he is going to do it is to adopt a formulary system, which means that some of the new, more expensive drugs will not be covered. These are drugs where there are no generic counterparts; they are still on patent, so they cannot have generic counterparts.

There was a specific provision in the Ways and Means bill in the House to authorize a formulary. The bill that finally passed the House is silent regarding formularies, and we believe there is inherent authority to use a formulary.

I believe we are about to reach an agreement in the Senate, and I will knock wood on that, that the Senate will include a provision in their version of the bill which will outlaw a formulary. If they do so, I could not make that statement in the ad; that would not be a true statement. But until it is done, and the House bill is what the ad concerns, and it is a true statement.

Senator METZENBAUM. Thank you very much, Mr. Mossinghoff and Dr. Jennings.

Senator Thurmond.

Senator THURMOND. I just have a couple of questions of Mr. Mossinghoff.

Would you explain the basis for membership in the PMA and the number of PMA companies which have generic subsidiaries or divisions, and what percentage of generic sales do these companies represent?

Mr. MOSSINGHOFF. Mr. Chairman, in answer to your first question, to become a member of the Pharmaceutical Manufacturers Association, a pharmaceutical company has to do a significant amount of research and development in the United States.

In response to your second question as to how many of our companies have generic subsidiaries, I would like to provide that answer for the record. I do not know the answer at this point, but I would be pleased to provide that answer to you for the record.

In response to your third question on what percentage of generics are made by PMA companies, the best information I have now is that the percentage is about 55 or 56 percent of the generics sold in the United States are sold by the member companies of the Pharmaceutical Manufacturers Association.

Senator THURMOND. Mr. Mossinghoff, what is the reaction of these companies, if you know, to antigeneric activity?

Mr. MOSSINGHOFF. Well, PMA does not have an antigeneric activity, Mr. Chairman. That is not something that PMA has done. We are concerned about the standards used by the Food and Drug Administration. We are concerned, because of those standards, about people being switched from one version of a drug to another version, but we do not have an anti-generic campaign.

Senator THURMOND. Mr. Chairman, that is all I have.

Senator METZENBAUM. Thank you very much.

Senator THURMOND. Thank you very much.

Senator METZENBAUM. Thank you, Mr. Mossinghoff, and thank you, Dr. Jennings.

[Statement and response to questions follow:]

Statement

Pharmaceutical
Manufacturers
Association

GERALD J. MOSSINGHOFF
PRESIDENT, PHARMACEUTICAL MANUFACTURERS ASSOCIATION

BEFORE THE

SUBCOMMITTEE ON ANTITRUST, MONOPOLIES AND BUSINESS RIGHTS
COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

OCTOBER 21, 1987

Mr. Chairman and Members of the Subcommittee:

I am Gerald J. Mossinghoff, President of the Pharmaceutical Manufacturers Association. PMA represents more than 100 research-based pharmaceutical companies that discover, develop and produce most of the prescription medicines used in the United States. I am accompanied this morning by Dr. John Jennings, PMA's Vice President for Science and Technology.

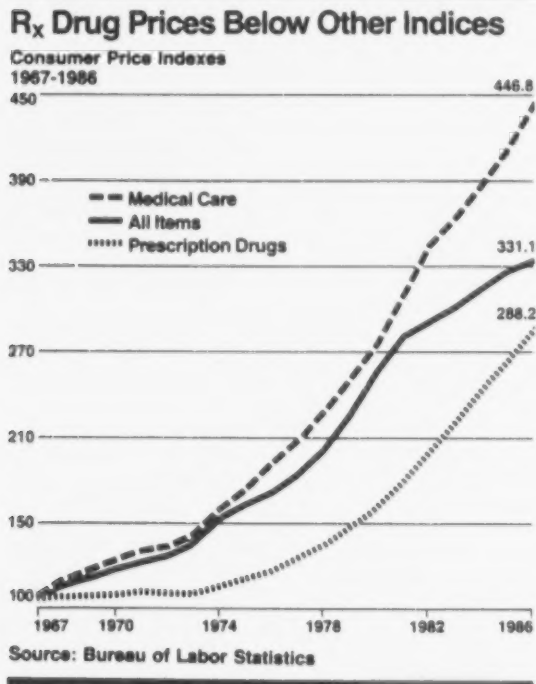
SUMMARY

Mr. Chairman and Members of the Subcommittee, I would like to make the following points in this brief summary:

- (1) First, let me say that our way of life in the United States would be unimaginable without the modern medicines discovered and developed by the PMA companies through their research and development. During 1986, PMA companies invested \$4.6 billion in R&D, an increase of 12 percent over 1985. People are living longer, healthier and more productive lives as a direct result of that investment. In recent years, the costs of providing health care, and the prices charged, have risen substantially. The same is true for prescription drugs. But modern prescription drugs are a very good value. Prescription drug prices have remained well below the overall Consumer Price Index ever since that index was set at 100 in 1967. And drug prices today are less than two-thirds the overall price index for medical care (Figure 1).

- 3 -

Figure 1

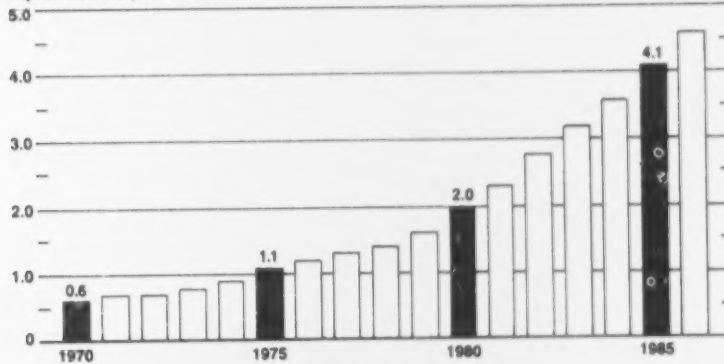


- (2) Research and development are the hallmarks of the PMA member companies. Their investment in R&D continues to double every five years (Figure 2). This year the industry will spend \$5 billion in discovering and developing new life-saving medicines, at an average cost of \$125 million for each new drug. There would, of course, be few generic drugs without the huge investment by the research-based pharmaceutical industry in discovering and developing new drugs and in educating physicians and other health-care professionals to use them properly and effectively.

Figure 2

PMA Company R&D Dollars Double Every 5 Years

Expenditures (\$ Billions)

Source: PMA Annual Survey

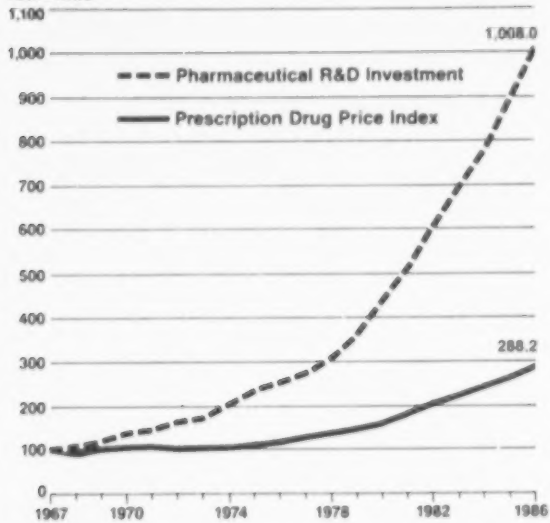
- (3) The industry is investing an increasingly higher percentage of sales--currently 15 percent--to finance its growing investment in R&D. Measuring increases in R&D expenditures the same way we measure price increases, the "index" for R&D conducted by PMA companies now stands at over 1,000, three and one-half times the prescription drug CPI (Figure 3).

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Figure 3

Increases in R&D Far Exceed Increases in Drug Prices

R_x R&D Index and
Consumer R_x Price Index
1967-1986



Source: PMA Annual Survey and Bureau of Labor Statistics.

- (4) There obviously is a place in the U.S. free-market economy for generic copies of pioneer drugs whose patents have expired. PMA is concerned, however, that generic drugs have been approved for marketing that are not in practice therapeutically equivalent to the pioneer products. Despite the claim of the Food and Drug Administration that it is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the Agency as bioequivalent, there are many examples where

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generic drugs produced different clinical results than the pioneer products. The details of specific reports are set forth in the Appendix to this statement, which I will submit for the record of these hearings.

In one drug-switching example cited in the Appendix, reported by a physician in the Journal of the American Medical Association, Vol. 258, No. 9, Sept. 4, 1987, a 16 year-old girl who had been stable on the same anti-epileptic medication for nine years suffered a dramatic increase in her seizure frequency after being switched to a generic drug. The physician stated: "In defense of the new regulations, the Food and Drug Administration (FDA) stated it 'is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the Agency as bioequivalent.' Our patient provides such a case."

- (5) PMA is particularly concerned about the indiscriminate switching of drug products, whether from brandname to generic, generic to brandname or from one generic to another. Patients on maintenance regimens whose daily dosage must be individualized are especially at risk when drug products are changed. Many such drugs are given to elderly patients and patients whose illnesses, such as heart failure or diabetes, can have life-

- 7 -

threatening consequences if treatment is inadequate. Many maintenance drugs require dose titration because of factors such as inter-patient variability, the shape of the dose response curve, the therapeutic index of the drug and the variable clinical course of the disease. The case reports in the Appendix demonstrate that patients with epilepsy, diabetes, cardiac disease and hyperactivity experienced problems following a switch from one version of a drug to another.

- (6) The FDA itself has acknowledged that, of the 6,000 marketed generic drugs listed in its Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the "Orange Book"), about 20 percent have not been determined by the Agency to be therapeutically equivalent to the pioneer products. Many physicians and pharmacists are unaware that FDA assigns different therapeutic ratings to marketed products, and thus do not use this information in prescribing and dispensing. This obviously raises a serious question as to why more than 1,000 drugs--that have neither been tested for safety and efficacy nor determined by FDA to be bioequivalent to pioneer products that have been so tested--are allowed to remain on the market.
- (7) PMA believes that the process used by the FDA to approve generic drugs needs to be improved. Indeed,

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the FDA itself has stated that its testing procedures for approving generic drugs can be improved. PMA believes that the FDA should (1) tighten the standards it uses to determine bioequivalence, by repudiating the across-the-board plus-or-minus 20 percent rule in favor of individualized drug-by-drug bioequivalence criteria; (2) use existing FDA surveillance systems to collect and evaluate bioequivalence data on generic products, and (3) extend FDA's warning about the risks of switching drugs--for drugs approved between 1938 and 1962--to all maintenance drugs approved through bioequivalence testing and include this caution in the product labeling, until such testing is scientifically demonstrated to assure safety and effectiveness.

- (8) Competition within the research-based pharmaceutical industry is intense. Among PMA members, no company commands more than 7 percent of total sales in the U.S., and the top 20 companies combined have less than 75 percent of U.S. sales. Through June 1987, 904 Abbreviated New Drug Applications (ANDAs) had been approved for marketing since enactment of the Drug Price Competition and Patent Term Restoration Act of 1984. The relatively new industry of companies that produce only generic drugs has captured an increasingly large share of the prescription-drug market and is highly profitable. This new industry, far from

suffering, is in fact thriving.

Mr. Chairman, that concludes the summary portion of my statement. The points I have made are developed more fully in the rest of my statement.

STATEMENT

In our free-enterprise system, there obviously is a role for generic copies of pioneer drugs after the patents on those pioneer drugs have expired. PMA is concerned, however, that the FDA is approving some generic drugs for marketing that are not in practice therapeutically equivalent to the pioneer products under all conditions of use. Because all states permit, or even mandate, substitution, patients may be switched not only from a brandname to a generic drug, but also from one generic to another and from a generic to a brandname drug.

To be approved by FDA, a generic drug must be shown to be bioequivalent to a brandname product--that is, it must be shown that the generic and pioneer drugs can be expected to have the same therapeutic effect when administered to patients under the conditions specified in the labeling. This is done not by testing the generic drug in patients with the condition for which the innovator's product was tested and approved by FDA, but by testing the generic in 16 to 20 healthy young men and comparing blood levels of the generic and innovator products. This

approach may suffice for many clinical situations, but it does not adequately assure safety and effectiveness under all expected conditions of use.

In the November 1986 FDA Drug Bulletin, the FDA stated: "FDA is not aware of a single documented case of bioinequivalence involving any generic drug product that has been approved by the Agency as bioequivalent." FDA has repeatedly made this claim, concluding, therefore, that there are no problems with the approval process. We believe, however, that a number of patients have suffered as a result of the random switching of multisource drugs. The details of specific case reports are set forth in the Appendix to this statement, which will be submitted for the record of these hearings.

In the last few months alone, medical journals have reported that product substitution has resulted in breakthrough epileptic seizures, toxic effects from psychotropic drugs and loss of diabetic control. FDA has rejected similar reports because they are not supported by blood level determinations or data from controlled clinical trials--criteria appropriate for a clinical trial, but not for an adverse drug experience report.

Our primary concern is that, with drugs used in a maintenance regimen where the dosage must be individually adjusted, patients are especially at risk when drug products are switched. Many such patients are elderly; the illness, such as

heart failure or diabetes, can have life-threatening consequences if treatment is inadequate; and side-effects or over-dosage can be serious. Many maintenance drugs require dose titration because of factors such as inter-patient variability, the shape of the dose response curve, the narrow therapeutic index of the drug and the variable clinical course of the disease.

In one drug-switching case, cited in the Appendix and reported by a physician in the Journal of the American Medical Association, Vol. 258, No. 9, Sept. 4, 1987, a 16 year-old girl who had been stable on the same anti-epileptic medication for nine years suffered a dramatic increase in her seizure frequency after being switched to a generic drug. The physician stated: "In defense of the new regulations, the Food and Drug Administration (FDA) stated 'it is not aware of a single documented case of bioequivalence involving any generic drug product that has been approved by the Agency as bioequivalent.' Our patient provides such a case."

In another case cited in the Appendix, which will be reported in a forthcoming issue of Neurology, a young epileptic woman suffered her first seizure in three years a few days after being switched to a generic drug. She was driving home from school at the time of her attack, and her car left the highway and struck a street sign.

In a third case cited in the Appendix and reported by a

physician in Diabetes Care, Vol. 10, No. 1, 1987, 14 diabetic patients who had been stable on the brandname product experienced significant increases in blood sugar levels when switched to the generic product. "It does not represent a controlled prospective clinical study," the physician wrote, "but rather a retrospective series of cases in which loss of clinical control has been attributed to generic substitution."

The FDA itself acknowledged that many generic drugs on the market are not therapeutically equivalent to the pioneer products. In the November 1986 FDA Drug Bulletin, the agency stated:

"FDA recommends generic substitution only among products that it has evaluated as being therapeutically equivalent. Since 1980, the Agency has published an annual Approved Drug Products with Therapeutic Equivalence Evaluations (also known as the "Orange Book"). This publication is updated monthly and contains information on more than 8,000 approved prescription drug products. Of these, about 6,000 are available from more than one manufacturer. Of the latter, more than 80 percent are evaluated as therapeutically equivalent."

Thus, nearly 20 percent of the multisource drugs on the market (or more than 1,000 drugs) are not considered therapeutically equivalent to the pioneer products.

Many physicians and pharmacists are unaware that FDA assigns different therapeutic ratings to marketed products, and thus do not use this information in prescribing and dispensing. The agency's disclaimer that it is unaware of any problems with drugs

it has determined to be bioequivalent does not even apply to these more than 1,000 generic drugs. A serious public-health question is raised as to why these drugs--that have neither been tested for safety and efficacy nor determined by FDA to be bioequivalent to those that have been so tested--are allowed to remain on the market.

As PMA pointed out in detail in its formal submission to the FDA during the agency's 1986 Hearing on Bioequivalence of Solid Oral Dosage Forms, we believe the procedures used by the FDA to approve generic drugs are inadequate and need to be improved. The FDA itself, in the notice for this hearing, stated that its testing procedures could be improved: "Bioequivalence testing based upon pharmacokinetic principles is a comparatively new and evolving science and, as such, the current methodology employed in the design and evaluation of bioequivalence trials could be further improved." Representatives of PMA member companies attended the bioequivalence hearing and presented our views. We have given the Subcommittee copies of the PMA presentations at the FDA hearing, together with three letters to FDA Commissioner Frank E. Young outlining our recommendations for improving the generic-approval process. You may wish to include these materials in the record of these hearings.

We do not believe that, under the current procedures, acceptable assurances can be provided that two formulations determined to be bioequivalent will be equally safe and equally

effective when used interchangeably by patients. A new formulation is allowed to exhibit up to a 20 percent variation in bioavailability in comparison to a pioneer product. Whether a 20 percent variation would adversely affect either clinical safety or effectiveness is often difficult to assess, and will likely depend on characteristics of the specific drug and patient. We believe, therefore, that the across-the-board plus-or-minus 20 percent rule should be discarded in favor of individualized drug-by-drug bioequivalence criteria developed by the FDA at the time a generic product becomes eligible for approval.

In addition, we believe the FDA should improve its existing surveillance system and employ other post-marketing studies to collect data on possible problems with multisource drugs. It is uncharacteristic of the agency to dismiss the mounting number of reports of possible therapeutic failures as anecdotal and, therefore, not worthy of investigation.

Further, we believe the FDA should extend its warning about the risks of switching drugs to all maintenance drugs approved through bioequivalence testing, and should include this warning in the product labeling. The FDA, in its November 1986 FDA Drug Bulletin, cautioned physicians about the potential hazards of switching among products approved between 1938 and 1962, noting that retitration may be required. We believe concern for patient safety should be extended to cover all approved multisource drugs that are used in maintenance therapy, until bioequivalence

testing is scientifically demonstrated to assure safety and effectiveness.

We also believe the FDA should take several other steps to improve the generic-approval system, which are outlined in the materials we have submitted to the Subcommittee.

We now turn to other matters of interest to the Subcommittee. On the subject of pharmaceutical research and development, this country's free-market system has created a favorable climate for our industry's R&D efforts. Our industry's investment in research and development has doubled every five years since 1970. PMA member companies currently are spending more than \$5 billion a year on research and development, at an average cost of \$125 million for each new drug.

Through the years, our companies have devoted an increasing proportion of their sales to R&D, and now are spending an estimated 15 percent of sales on research and development. Next year, PMA companies will spend more on pharmaceutical R&D than all of the Institutes of the National Institutes of Health will spend on all biomedical research. Using new and exciting knowledge about molecular biology and new methods of research and development, our companies are developing new treatments and cures for such diseases as cancer, heart disease, Alzheimer's disease, leukemia and AIDS. Congress should preserve the climate in this country that encourages research-based companies to

discover and develop these and other new life-saving medicines.

Our industry, despite its relatively small size, ranked fourth last year behind the aircraft, plastics and office machinery industries in contributing a positive balance of trade among the ten high-technology industries tracked by the Commerce Department. Our industry recorded a positive balance of trade of \$764 million in 1986, a year when the ten high-technology industries as a whole had a negative balance of trade for the first time, of \$2.6 billion. Spurred by our free-enterprise system, our industry has been a world leader in developing new drugs, but this leadership is being challenged by foreign companies.

Competition is intense within the research-based pharmaceutical industry. No company commands more than 7 percent of total sales in the U.S., and the top 20 companies combined have less than 75 percent of U.S. sales. Through June 1987, 904 Abbreviated New Drug Applications (ANDAs) for generic drugs had been approved for marketing since enactment of the Drug Price Competition and Patent Term Restoration Act of 1984. During the first six months of 1987, the FDA approved an average of 40 ANDAs per month. Generic drugs usually capture 30 percent to 40 percent of the market within two years of their introduction, and sales of generic products currently represent about 25 percent of the prescription-drug market. By 1991, generic sales are projected to represent about one-third of the market.

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Federal programs are accelerating the use of generic drugs by speeding generic approvals at the FDA and by including generic product-selection incentives in government reimbursement programs. The Health Care Financing Administration published rules recently that encourage pharmacists to dispense generics for Medicaid patients. The House passed legislation (H.R. 2470) this summer that would encourage the use of generic drugs by Medicare outpatients. As a result, the relatively new industry of companies that produce only generic drugs has captured an increasingly large share of the prescription drug market and is highly profitable. This new industry, far from suffering, is in fact thriving.

Mr. Chairman, that concludes my full statement. I would be pleased to answer any questions you or other members of the Subcommittee may have.

Gerald J. Mossinghoff
PRESIDENT

**Pharmaceutical
Manufacturers
Association**

November 17, 1987

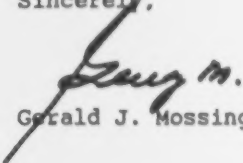
The Honorable Strom Thurmond
United States Senate
Washington, D.C. 20510

Dear Senator Thurmond:

Enclosed are my answers for the record to two questions you asked me at the hearing on October 21, 1987 held by the Subcommittee on Antitrust, Monopolies, and Business Rights on competitive problems in the pharmaceutical drug industry.

Please let me know if you have any other questions or if I can be of help in any other way.

Sincerely,



Gerald J. Mossinghoff

Enclosures

cc: Ms. Mary Louise Westmoreland

1. Question: "State the number of PMA companies which have generic subsidiaries or divisions."

Answer: The following members of the Pharmaceutical Manufacturers Association or their subsidiaries sell generic drugs:

Astra Pharmaceutical Products, Inc.
 Wyeth Laboratories
 Beecham Laboratories
 Roxane Laboratories, Inc.
 The Boots Company (USA) Inc.
 Bristol-Myers U.S. Pharmaceutical and Nutritional Group
 Geneva Generics (Ciba-Geigy Corporation)
 Cord Laboratories (Ciba-Geigy Corporation)
 Lederle Laboratories
 Eli Lilly and Company
 Pfizer Inc.
 Roerig (Pfizer Inc.)
 Elkins Sinn (A. H. Robins Company)
 Rorer U.S.
 G.D. Searle & Co.
 Smith Kline & French Laboratories
 Warner Chilcott (Warner-Lambert Company)
 Parke Davis
 Squibb Corporation
 E. Fougera & Company
 Savage Laboratories

Note: Parent company for non-member subsidiaries is shown in parentheses.

2. Question: "What percentage of generic sales do PMA member companies and their subsidiaries or divisions represent?"

Answer: In 1986, according to IMS America data, PMA members accounted for 56 percent of the dollar volume of sales of generic versions of pioneer products.

Gerald J. Mossinghoff
PRESIDENT

November 17, 1987

**Pharmaceutical
Manufacturers
Association**

The Honorable Howard M. Metzenbaum
Chairman, Subcommittee on Antitrust,
Monopolies, and Business Rights
Committee on the Judiciary
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

During my testimony before your Subcommittee on Antitrust, Monopolies, and Business Rights on October 21, you asked whether the Pharmaceutical Manufacturers Association might set ethical marketing standards for the research-based pharmaceutical industry. I stated that I would discuss your suggestion with the PMA Executive Committee.

At its meeting on November 12, our Executive Committee decided to have appropriate PMA Sections and the PMA staff review existing PMA marketing guidelines to consider whether any changes might be necessary.

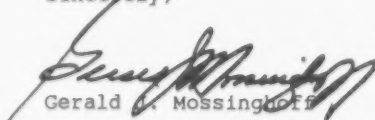
As pointed out in response to the questions you sent me on November 2, PMA has adopted three codes of marketing practices:

- The Code of Fair Practices In The Promotion of Drug Products, adopted in 1967.
- The IFPMA Code of Pharmaceutical Marketing Practices, adopted in 1982.
- The Voluntary Code for Prescription Drug Sampling Practices, adopted in 1986.

Copies of these three codes are enclosed.

I will keep you advised of further developments regarding our review of our marketing codes.

Sincerely,


Gerald J. Mossinghoff

Enclosures

PMA Voluntary Code for Prescription Drug Sampling Practices

**Pharmaceutical
Manufacturers
Association**

Many pharmaceutical companies, in response to requests, provide health practitioners with prescription medication samples or patient starter packages. The Pharmaceutical Manufacturers Association (PMA) strongly supports this system of prescription medication sampling primarily through the professional representative. The system is beneficial to patients, physicians, the health care system, and the pharmaceutical industry.

Patient starter packages enable a physician to begin immediately to evaluate the effect of a prescription product in a patient who has been newly-diagnosed and to identify early any side effects. If a pharmaceutical product is not working as intended or is not tolerated, the medication can be changed or the dosage modified without expense to the patient. Samples also enable physicians to initiate therapy immediately where patients are in pain or are developing infections.

Discussions between a physician and a patient on how to take a prescription medication at the time a sample is dispensed, can improve a patient's compliance. The current system of sampling fosters competition within the pharmaceutical industry by allowing companies both to educate practitioners on the use of newly-introduced products and to familiarize new practitioners with products already on the market. Finally, personal delivery of samples allows manufacturers' representatives and practitioners to discuss appropriate use of pharmaceutical products and permits practitioners to begin using samples immediately, while these discussions are fresh in mind.

The following Voluntary Code for Prescription Drug Sampling Practices was adopted by PMA to reduce the potential for diversion of pharmaceutical samples into illicit markets and to bring greater controls to the current sampling system by strengthening sound sampling practices. This will obviate the need for changing a system that has served well for many decades.

PMA members hereby declare their intention to conform voluntarily to the following Code of Prescription Drug Sampling Practices:

-
1. **Distribution**—Companies will distribute samples only to licensed practitioners pursuant to written request or receipt on each sampling occasion. The request or receipt will contain the practitioner's name, address, professional designation, the identity and quantity of samples requested, the name of the company, and the dated signature of the practitioner.
 2. **Storage**—Effective controls and procedures to guard against theft and diversion of samples will be maintained at all times. All samples will be stored in cabinets, storage areas, or rooms which are appropriately secured and accessible only to company representatives or other authorized persons. Companies will direct their employees to store samples under conditions that will maintain their stability, integrity, and effectiveness.
 3. **Disposal**—All outdated or damaged samples will be returned to the company for disposal.
 4. **Inventory**—Companies will require that a complete and accurate inventory of all samples in the possession of a company representative be conducted at least annually by an agent of the company other than the representative in possession of the samples.
 5. **Record Keeping**—Lists will be maintained of the names and addresses of all individuals who distribute samples and of all sites where samples are stored. Companies will maintain records for at least two years of all samples distributed, destroyed, or returned to the company, of all inventories, of all thefts or significant losses, and of all requests and receipts for samples.
 6. **Cooperation with Government Officials**—Companies will notify the appropriate government authority of any significant theft, diversion, or loss of samples. Records maintained pursuant to paragraph 5 will be made available to appropriate government authorities upon a showing of reasonable cause. Companies will provide the name and telephone number of the individual responsible for responding to requests for information made by government authorities.

IFPMA CODE
OF PHARMACEUTICAL
MARKETING PRACTICES

CODE FIIM
DE PRATIQUES
DE COMMERCIALISATION
DES PRODUITS
PHARMACEUTIQUES

CODIGO FIIM
DE NORMAS
DE COMERCIALIZACION
DE PRODUCTOS
FARMACEUTICOS

INTERNATIONAL FEDERATION OF PHARMACEUTICAL
MANUFACTURERS ASSOCIATIONS (IFPMA)

FEDERATION INTERNATIONALE DE L'INDUSTRIE
DU MEDICAMENT (FIIM)

FEDERACION INTERNACIONAL DE LA INDUSTRIA DEL
MEDICAMENTO (FIIM)

IFPMA CODE OF PHARMACEUTICAL MARKETING PRACTICES

The INTERNATIONAL FEDERATION OF PHARMACEUTICAL MANUFACTURERS ASSOCIATIONS (IFPMA) is a nongovernmental organization having as its members, direct or through regional organizations, the pharmaceutical industry associations of 50 countries in all parts of the world. The Federation was founded in 1968 and was admitted into official relations with the World Health Organization in 1971. It has since then obtained consultative status with the World Intellectual Property Organization, the United Nations Industrial Development Organization, the United Nations Conference on Trade and Development, the U.N. Economic and Social Council, the United Nations Children's Fund (UNICEF) and the Council of Europe.

The objects of the Federation are:

- a. to assure permanent contact among its members;
- b. to deal with all questions of common interest, for example, in the fields of health legislation, science and research, in order to contribute to the advancement of the health and welfare of the peoples of the world;
- c. to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on;
- d. to contribute expertise to, and to cooperate with, national and international organizations, governmental or non-governmental, having the same aims; and
- e. to coordinate the efforts of its members towards the realization of the above objects.

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Preamble

The Statute of the Federation article 3 states that one of the objects of the Federation is «to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on» and «to coordinate the efforts of its members towards the realization of the above objects».

It is believed that in keeping with the pharmaceutical industry's international responsibilities, the members of the Federation will be prepared to accept certain obligations, insofar as their marketing practices are concerned, and to ensure respect for them.

IFPMA recommends a Code of Marketing Practices to its member associations, recognizing the difficulty of setting out a simple Code which will be applicable in all parts of the world. It seems clear that national and regional conditions and legal restrictions will continue to vary to such an extent as to make a simple world Code impractical. Nevertheless, the Federation believes that it has a duty to encourage its member associations to either introduce such Codes of Practices or where such Codes already exist, to continually re-examine and where necessary revise them so that a voluntary system based on such a Code keeps pace with modern medical knowledge and changing health services and conditions.

It is recognized that many individual member associations of IFPMA have laid down their own Codes of Marketing Practices and this recommended Code is not intended to replace similar Codes or instruments already in force by members of the Federation. The following voluntary Code is therefore put forward as a model for IFPMA's member associations.

A Code of Marketing Practices of this sort should be the responsibility of member associations who should also provide guidance to their members on matters of compliance and interpretation.

Obligations of Industry

The obligations of the industry may be identified as follows:

The pharmaceutical industry, conscious of its special position arising from its involvement in public health, and justifiably eager to fulfil its obligations in a free and fully responsible manner, undertakes:

- to ensure that all products it makes available for prescription purposes to the public are backed by the fullest technological service and have full regard to the needs of public health;
- to produce pharmaceutical products under adequate procedures and strict quality assurance;
- to base the claims for substances and formulations on valid scientific evidence, thus determining the therapeutic indications and conditions of use;
- to provide scientific information with objectivity and good taste, with scrupulous regard for truth, and with clear statements with respect to indications, contra-indications, tolerance and toxicity;
- to use complete candour in dealings with public health officials, health care professionals and the public.

Suggested Code of Marketing Practices

We hereby declare our intention to voluntarily conform to the following Code of Marketing Practices:

1. General Principles

1. The term "pharmaceutical product" in this concept means any pharmaceutical or biological product intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans, or to affect the structure or any function of the human body, which is promoted and advertised to the medical profession rather than directly to the lay public.
2. Information on pharmaceutical products should be accurate, fair and objective, and presented in such a way as to conform not only to legal requirements but also to ethical standards and to standards of good taste.
3. Information should be based on an up to date evaluation of all the available scientific evidence, and should reflect this evidence clearly.
4. No public communication shall be made with the intent of promoting a pharmaceutical product as safe and effective for any use before the required approval of the pharmaceutical product for marketing for such use is obtained. However, this provision is not intended to abridge the right of the scientific community and the public to be fully informed concerning scienti-

fic and medical progress. It is not intended to restrict a full and proper exchange of scientific information concerning a pharmaceutical product, including appropriate dissemination of investigational findings in scientific or lay communications media, nor to restrict public disclosure to stockholders and others concerning any pharmaceutical product as may be required or desirable under law, rule or regulation.

5. Statements in promotional communications should be based upon substantial scientific evidence or other responsible medical opinion. Claims should not be stronger than such evidence warrants. Every effort should be made to avoid ambiguity.
6. Particular care should be taken that essential information as to pharmaceutical products' safety, contraindications and side effects or toxic hazards is appropriately and consistently communicated subject to the legal, regulatory and medical practices of each nation. The word "safe" must not be used without qualification.
7. Promotional communications should have medical clearance, or where appropriate, clearance by the responsible pharmacist, before their release.

II. Medical Representatives

Medical representatives must be adequately trained and possess sufficient medical and technical knowledge to present information on their company's products in an accurate and responsible manner.

III. Symposia, Congresses and other Means of Verbal Communication

Symposia, congresses and the like are indispensable for the dissemination of knowledge and experience. Scientific objectives should be the principal focus in arranging such meetings, and entertainment and other hospitality shall not be inconsistent with such objectives.

IV. Printed Promotional Material

Scientific and technical information shall fully disclose the properties of the pharmaceutical product as approved in the country in question based on current scientific knowledge including:

- The active ingredients, using the approved names where such names exist.
- At least one approved indication for use together with the dosage and method of use.
- A succinct statement of the side-effects, precautions and contraindications.

Except for pharmaceutical products where use entails specific precautionary measures, reminders need not necessarily contain all the above information (see *Second Supplementary Statement*, p. 23) providing that a form of words is used which indicates clearly that further information is available on request.

Promotional material, such as mailings and medical journal advertisements, must not be designed to disguise their real nature and the frequency and volume of such mailings should not be offensive to the health care professionals.

V. Samples

Samples may be supplied to the medical and allied professions to familiarize them with the products, to enable them to gain experience with the product in their practice, or upon request.

The Supplementary Statements which follow have been promulgated to clarify certain aspects of the operation and interpretation of the Code. They should be regarded as an integral part of the Code document. The texts are in English only.

First Supplementary Statement (March 1982)

IFPMA and its Member Associations agreed the following statement in March 1982 which they believe will further demonstrate the industry's commitment to the observance and monitoring of the Code. It should be emphasized however that this supplementary statement does not vary in any way the provisions of the original Code.

1. Major pharmaceutical multinational companies (MNCs) belonging to IFPMA Member Associations, have been asked to commit themselves to the observance of the Code wherever they market their products.
2. To meet the criticism that many Third World countries are not aware of the indications, contra-indications, side effects etc, of individual drugs that have been accepted in the developed countries, IFPMA will offer help to supply free of charge to Government Health Departments of Third World countries, copies of up-to-date standard compendia such as, The Physician's Desk Reference (USA), the ABPI's Data Sheet Compendium (UK), the Rote Liste (Federal Republic of Germany) and the Dictionnaire Vidal (France).
3. The following procedure has been agreed to deal with alleged breaches in the observance of the Code. IFPMA Member Associations have been recommended to set up their own separate procedures for monitoring such complaints; many of the major Associations have already done this. A procedure has also been agreed to deal with complaints received by IFPMA itself and an ex officio committee of IFPMA's Council consisting of the President, the two

Vice-Presidents and the Executive Vice-President will oversee all IFPMA matters involving the Code.

The major sanction against any company that transgresses the Code will continue to be the sanction of adverse publicity. However, IFPMA wishes to stress that its main objective and that of its Member Associations will be to effect, as rapidly as possible, the correction of any proven breaches in the observance of the Code.

4. Comments have been made from time to time about the problem that industry faces in providing uniform information worldwide on labelling, packaging leaflets, data sheets and general advertising claims. The industry's position on the important matters of information on scientific claims, contra-indications and side effects is set out in the Code itself. This makes it clear that labelling, packaging leaflets, the information and data sheets and advertising claims should be consistent with the body of scientific and medical evidence pertaining to that product. This should be interpreted as meaning that such information given in Third World countries, should be consonant with what is being done in the companies' markets in the developed world. However, it should be borne in mind that countries which have their own regulatory procedures (and this includes many Third World countries) may well dictate a non-uniform approach to such matters, which industry has no option but to follow.

The voluntary adoption of this IFPMA Code is in line with one of the key objectives of the Federation as set out by its Founder Members in 1968, «to promote and support continuous development throughout the pharmaceutical industry of ethical principles and practices voluntarily agreed on».

Second Supplementary Statement (March 1987)

At a meeting held in October 1983 IFPMA Council decided that Section IV of the IFPMA Code referring to Printed Promotional Material should be interpreted as requiring that all advertisements *including* reminder advertisements should specify the approved name(s) of the active ingredient(s) of the preparation. This decision was communicated to Member Associations at that time.

At a meeting of the IFPMA Council held in February 1987, it was resolved that this decision should be incorporated in the Code by means of a Second Supplementary Statement.

It was further resolved at the above mentioned meeting that, in interpreting the scope of the Code as it applied to products "promoted to the medical profession rather than to the general public" (Section 1.1. General Principles), the following clarification should apply: All promotion and advertisements of pharmaceutical products directed to the health care professions would be deemed to fall within the scope of the Code. But advertising of self medication products to the general public is excluded from the scope of the Code as is advertising to pharmacists where this is intended to support advertising to the public of such products.

IFPMA Member Associations

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Costa Rica, Guatemala, Honduras, Nicaragua, Panama, El Salvador)

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Telex 710-822-9494 pma wsh
Telefax (202) 835-3413

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Federación Latinoamericana de la Industria

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Gerald J. Mossinghoff
PRESIDENT

**Pharmaceutical
Manufacturers
Association**

November 17, 1987

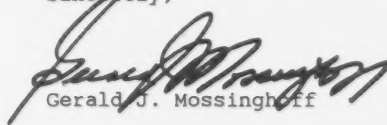
The Honorable Howard M. Metzenbaum
Chairman, Subcommittee on Antitrust,
Monopolies, and Business Rights
Committee on the Judiciary
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

Enclosed are my answers to your follow-up questions from the hearing held on October 21, 1987 by the Subcommittee on Antitrust, Monopolies, and Business Rights on competitive problems in the pharmaceutical drug industry.

Please let me know if you have any further questions.

Sincerely,


Gerald J. Mossinghoff

Enclosures

1. Question: "Does the PMA have marketing guidelines that it recommends for or requires of its members? If so, how were these established? When? Would you provide a copy of any such marketing guidelines to the Subcommittee?"

Answer: The Pharmaceutical Manufacturers Association adopted a Code of Fair Practices In The Promotion of Drug Products in 1967, a copy of which is attached. The Code was intended to apply to the practices and activities of PMA member companies within the United States. Copies of the Code were widely distributed to the member companies of PMA.

In 1981, the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), of which PMA is a member, adopted the IFPMA Code of Pharmaceutical Marketing Practices. In March 1982, PMA adopted the IFPMA Code, a copy of which is attached. The IFPMA Code also was widely distributed to member companies of PMA, with the recommendation that the principles of the Code be followed in marketing products outside of the United States.

In September 1986, PMA adopted a Voluntary Code for Prescription Drug Sampling Practices, a copy of which is attached. The Code was intended to reduce the potential for diversion of pharmaceutical samples into illicit channels and to bring greater controls to the current sampling system by strengthening sound sampling practices. This Code also was widely distributed to PMA member companies.

Code of Fair Practices

In The Promotion Of Drug Products

Recognizing the importance to the public health of providing the medical profession with accurate information on drug products, and the need to assure that PMA members, their employees and agents present such information fairly and objectively,

The Pharmaceutical Manufacturers Association hereby promulgates and adopts the following Code of Fair Practices in the Promotion of Drug Products as a revision of its 1958 Statement of Principles on the same subject:

A. Code Standards

1. As used in this Code:

(a) The term "drug product" means any pharmaceutical or biological product intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans, or to affect the structure or any function of the human body, which is promoted and advertised to the medical profession rather than directly to the lay public.

(b) The term "promotional communications" means (1) journal advertising, mailing pieces, and similar written materials (including, to the extent reasonably practicable, films, exhibits and similar

visual presentations) directed to members of the medical profession by the pharmaceutical industry for the purpose of promoting a drug product and (2) written instructions and materials prepared for sales or professional representatives containing representations to be made by them to members of the medical profession. Where compliance with the requirements of this Code is not reasonably practicable within the format of a film, exhibit or similar visual presentation, written materials meeting those requirements shall be distributed to all members of the medical profession attending the presentation.

(c) The term "medical profession" includes allied professions in the health field.

2. Complete and accurate information concerning marketed drug products should be made available promptly to the medical profession. Promotional communications to the medical profession which include a description of indicated uses or dosage recommendations for a prescription drug product should also include a summary (or full disclosure where required by law) of side effects, precautions, warnings and contraindications, and of effectiveness for the described indicated uses. Such summary should have sufficient prominence in terms of type size, location and similar factors to provide reasonable assurance that it will be observed.

3. Statements in promotional communications should be based upon substantial scientific evidence or other responsible medical opinion. Claims should not be stronger than such evidence warrants. Every effort should be made to avoid ambiguity. Whenever statistical or background information or references to unpublished literature or observations are used in promotional communications, the source material should be available to the medical profession upon request.

4. Statements with respect to or quotations from medical literature or from the personal communications of clinical investigators in promotional communications should not distort the intended meaning of the author or the significance of the study.

5. Any comparison with other drug products should be made upon a valid scientific basis.

6. No public communication by a manufacturer shall be made with the intent of promoting a drug product as safe and effective for any use before the required approval of the drug product for marketing for such use is obtained. However, this provision is not intended to abridge the right of the scientific community and the public to be fully informed con-

cerning scientific and medical progress. Thus it is not intended to restrict a full and proper exchange of scientific information concerning a drug product, including appropriate dissemination of investigational findings in scientific or lay communications media, nor to restrict public disclosure to stockholders and others concerning any drug product as may be required or desirable under law, rule or regulation.

7. Promotional communications should have medical clearance before their release.

B. Code Administration

It is the unqualified intent of the Association that each member shall follow strictly the principles set forth in the Code. To that end the members of the PMA are encouraged to submit information to the President with respect to any alleged breach of this Code by any other member. On the basis of such information and any other information available to him, the President shall take appropriate action including, if required, referral of the information to an ad hoc committee of the Board. The committee shall be chosen by the Chairman of the Board unless the member company represented by the Chairman has submitted such information or is the subject of such information, in which case the President shall make the appointments. The General Counsel of the Association shall act as secretary of each ad hoc committee and shall report the committee's findings to the President who in turn will refer the findings to the Board of Directors.

Any member firm which clearly and persistently violates the Code may be asked by the Board of Directors to resign from the Association.



Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W., Washington, D.C. 20005
(202) 296-2440

2. Question: "At the hearing, considerable testimony was given concerning the drugs given a "B" rating in the FDA's 'Orange Book'. Does the PMA believe that any of these drugs is unsafe? If so, please specify which drugs? Does the PMA contend that any of these drugs is ineffective? If so, please specify which drugs?"

Answer: Under the Federal Food, Drug, and Cosmetic Act, pioneer drugs are approved by the Food and Drug Administration as safe and effective under a New Drug Application (NDA) only after extensive clinical testing is conducted to determine safety and efficacy.

There are many "B" drugs that have neither been proven to be safe and effective under an NDA nor determined by the FDA to be therapeutically equivalent to approved pioneer products. We do not know whether these "B" drugs are safe and effective, but nevertheless they are substituted for safe and effective pioneer products and for other generic drugs that have been rated to be therapeutically equivalent to pioneer products. This situation creates a public health risk of unknown magnitude.

3. Question: "Which of these B rated drugs are manufactured by PMA members? Are the B rated drugs that are manufactured by PMA companies safer or more effective than those produced by non-PMA member companies?"

Answer: In the attached tabulation of drugs approved by the Food and Drug Administration on the basis of an Abbreviated New Drug Application (ANDA), the "B" drugs manufactured by members of the Pharmaceutical Manufacturers Association are marked by an asterisk. All of the other drugs on the list are manufactured by other companies.

None of the drugs on the tabulation have been clinically tested to prove safety and efficacy nor determined by the FDA to be therapeutically equivalent to pioneer drugs that have been so tested. The safety and efficacy of all of these drugs is unproven.

**Drugs Having Approved Abbreviated New Drug Applications
But Not Considered by FDA to be Therapeutically Equivalent to
Other Pharmaceutically Equivalent Products (B-Rated Drug
Products)¹**

<u>Product & Dosage Form</u>	<u>Firm</u>	<u>Rating²</u>	
Aminophyllin E.C. Tab.	Richlyn Tablicaps	BD	
Aminophyllin Tab.	Ascot Barr Chelsea Cord Halsey ICN KV Lannett Panray Phoenix Purepac Richlyn	BD	
Amitriptyline Tab.	AM Therapeutics Copley Halsey PAR Superpharm	BP	
Benzthiazide Tab.	Private Form	BP	
Benztropin	PAR Quantum	BP	
Caffeine; Ergotamine Supp.	Organon	BR	*
Chlorothiazide; Reserpine Tab.	West-Ward Bolar Mylan	BP	
Chlorpheniramine; Phenylpropanolamine CR Tab.	Ascher	BC	*

¹ Source: "Approved Drug Products with Therapeutic Equivalence Evaluations, 7th Edition, 1987." (Orange Book.)

² See Attachment A

* PMA Member Firm

Chlorpromazine Tab.	Lederle P-D Chelsea Cord KV Pharm Basics Private Form Vanguard West-Ward Zenith	BP	* *
Colchicine; Probenecid Tab.	Beecham Lederle Danbury Chelsea Richlyn Vitarine Zenith Bolar	BP	* *
Cortisone Acetate Inj.	Carter-G Lemmon	BP	
Cortisone Acetate Tab.	Barr Chelsea Heather Imwood Lannett Panray Purepac Quantum Richlyn Simpak West-Ward White TN Zenith	BP	
Deserpidine; Methyclothiazide Tab.	Bolar	BP	
Dexamethasone Tab.	Reid-Rowell Roxane Barr Bolar Chelsea Cord Danbury PAR Phoenix Private Form Richlyn Upsher-Smith White TN	BP	* *
Dexamethasone Ace. Inj.	Carter-G	BP	

Diethylstilbesterol Tab.	Tablicaps	BE	
Diethylstilbesterol EC Tab.	Tablicaps	BE	
Disulfiram Tab.	Chelsea Danbury PAR Sidmak	BX	
Diphyllin Tab.	Savage Wallace	BP	* *
Estrogens, Conj. Tab.	Chelsea Duramed Heather Private Form Zenith	BS	
Estrogens, Est. Tab.	Squibb Reid-Rowell Syntex Beecham Private Form	BS	* * * *
Estrone Inj.	Ayerst Carter-G	BP	*
Fluoxymesterone	Brown Bolar Colmed	BP	
Hydralazine; HCTZ Tab.	Chelsea Bolar	BP	
Hydralazine; HCTZ; Reserpine Tab.	Lederle Reid-Rowell Camall Mylan Zenith Vitarine Bolar Danbury Barr	BP	* *
Hydralazine; Reserpine Tab.	Vitarine	BP	

HCTZ; Reserpine Tab.	Roxane White TN Camall Vitarine Bolar Chelsea Danbury Zenith Barr Cord West-Ward	BP	*
Hydrocortisone Tab.	Vitarine Anabolic Barr Danbury Imwood Lannett MK Panray Purepac Quantum Richlyn West-Ward White TN	BP	
Hydrocortisone Ace. Inj.	Bel-Mar Carter-G Lemmon	BP	
Hydroflumethiazide; Reserpine Tab.	Colmed PAR Bolar Zenith	BP	
Imipramine Tab.	Smith Kline	BP	*
Isoetharine Mes. INH	Natl Pharm	BN	
Isoproterenol HCAscot INH.	Natl Pharm	BN	
Medroxyprogesterone Ace. Tab.	Reid-Rowell Colmed Carnrick	BP	*
Methoxsalen Cap.	Cord	BP	
Methylprednisolone Tab.	Chelsea Duramed Heather Vitarine	BP	

Methylprednisolone Inj.	Bel-Mar Carter-G Lemmon Maurry	BP	
Methyltestosterone Caps.	Heather ICN Star	BP	
Methyltestosterone Buc.	Lilly Pharm Basics Private Form Richlyn Tablicaps	BP	*
Methyltestosterone Tab.	Lilly Danbury Imwood KV Lannett Private Form Purepac Richlyn Tablicaps West-Ward	BP	*
Orphenadrine CR	Cord	BC	
Phendimetrazine C.R. Tab.	Reid-Rowell Cord DM Graham Rexar	BC	*
Phenytoin Prompt Caps.	Lannett Chelsea Danbury Zenith	BX	
Phytonadione Inj.	Beecham Abbott Intl Med	BP	* *
Prednisolone Tab.	Roxane Ferndale Halsey Barr Bell Chelsea CM Bundy Cord Danbury Heather ICN Imwood Lannett	BX	* *

	Lemmon		
	Marshall		
	Panray		
	Phoenix		
	Private Form		
	Purepac		
	Quantum		
	Richlyn		
	Simpak		
	Sperit		
	Superpharm		
	Tablicaps		
	Unit Dose Labs		
	Vitarine		
	West-Ward		
	White TN		
	Zenith		
Prednisolone Ace. Inj.	Central	BP	*
	Bel-Mar		
	Carter-G		
	Lemmon		
	Maurry		
Prednisolone Terb. Inj.	Carter-G	BP	
Prednisone Tab.	Miles	BX	*
	Lederle		*
	Roxane		*
	Ferndale		*
	Halsey		
	Barr		
	Bell		
	Chelsea		
	CM Bundy		
	Cord		
	Danbury		
	Heather		
	ICN		
	Imwood		
	Lannett		
	Lemmon		
	Marshall		
	Panray		
	Phoenix		
	Private Form		
	Purepac		
	Quantum		
	Richlyn		
	Simpak		
	Sperit		
	Superpharm		
	Tablicaps		
	Unit Dose Labs		
	Vitarine		
	West-Ward		

	White TN		
	Zenith		
	Forest		
	First Texas		
	KV		
	MK		
	Pharmavite		
	Rexall		
	Upsher-Smith		
	Vanguard		
Procainamide C.R. Tab.	Squibb	BC	*
Promethazine Supp.	Alcon	BR	*
Promethazine Tab.	Dupont	BP	*
	Barr		
	Bolar		
	Chelsea		
	Cord		
	Danbury		
	Lannett		
	Lemmon		
	Private Form		
	Richlyn		
	Tablicaps		
	Vitarine		
	Zenith		
Propylthiouracil Tab.	Anabolic	BD	
	Barr		
	Bell		
	Chelsea		
	Danbury		
	Halsey		
	Lannett		
	Purepac		
	Richlyn		
	Tablicaps		
	West-Ward		
	Zenith		
Quinidine Gluc. C.R. Tab.	Lannett	BC	
Rauwolfia	Squibb	BP	*
Serpentina	Reid-Rowell		*
	Danbury		
	Halsey		
	Private Form		
	Purepac		
	Tablicaps		
Reserpine Tab.	Reid-Rowell	BP	*
	Barr		
	Bell		
	Chelsea		

	Danbury		
	Halsey		
	Lemmon		
	Marshall		
	MX		
	Mylan		
	Pharmavite		
	Private Form		
	Purepac		
	Quantum		
	Rexall		
	Tablicaps		
	West-Ward		
	White TN		
Reserpine;	Bolar	BP	
Trichlormethiazide Tab.			
Sulfasalazine Tab.	Vitarine	BP	
Sulfasalazine E.C. Tab.	Bolar	BE	
Sulfisoxazole Tab.	Chelsea		
Theophyllin Cap.	Winthrop	BP	*
	Schering	BX	*
	Fisons	BP	*
	Scherer		*
	KV		
Theophyllin C.R. Caps.	Schering	BC	*
	Rorer		*
	Fisons		*
	Central		*
	Searle		*
	Glaxo		*
	McNeil		*
	Scherer		*
	Fleming		
	Key		
	Vitarine		
Theophyllin Tab.	Central	BD	*
	Riker		*
Theophyllin C.R. Tab.	Mead Johnson	BC	*
	Pfizer		*
	P-F		*
	Key		
	Forest		
Thyroglobulin Tab.	Richlyn	BP	
Triamcinolone Tab.	Roxane	BP	*
	Barr		
	Chelsea		

	Danbury Lemmon Mylan Purepac Richlyn Zenith	
Triamcinolone Diace. Inj.	Carter-G Lemmon Maurry	BP
Triamcinolone Acetonide Inj.	Carter-G	BP
Trichlormethazide Tab.	Lannett MM Mast Bolar Camall Chelsea Danbury PAR Richlyn Vitarine	BP
Warfarin Sod. Tab.	Bolar	BX

"B CODES"

Drug products that FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products.¹

- BC - Controlled-release tablets, controlled-release capsules, and controlled-release injectables
- BD - Active ingredients and dosage forms with documented bioequivalence problems
- BE - Enteric-coated oral dosage forms
- BN - Products in aerosol-nebulizer drug delivery systems
- BP - Active ingredients and dosage forms with potential bioequivalence problems
- BR - Suppositories or enemas for systemic use
- BS - Products having drug standard deficiencies
- BT - Topical products with bioequivalence issues
- BX - Insufficient data

¹ Source: "Approved Drug Products with Therapeutic Equivalence Evaluations, 7th Edition, 1987". (Orange Book).

4. Question: "How much money has the PMA spent to promote or advertise the study which appeared in the November 14, 1986 Journal of the American Medical Association comparing prices of generic and name brand drugs? Please list any PMA publication or article prepared or funded by the PMA that discusses the study."

Answer: The Pharmaceutical Manufacturers Association has not spent any money to promote or advertise the study that appeared in the November 14, 1986 Journal of the American Medical Association.

The study was mentioned by Robert F. Allnutt, Executive Vice President of PMA, in testimony on June 2, 1987 before the House Ways and Means Subcommittee on Health and the House Energy and Commerce Subcommittee on Health and the Environment at hearings on outpatient prescription-drug coverage under Medicare. The study also was mentioned by PMA President Gerald J. Mossinghoff in a letter to the editor of Consumer Reports on July 17, 1987.

5. Question: "Has the PMA ever provided funds to The National Alliance of Senior Citizens in connection with any educational or legislative campaign at the local, state or federal level?"

Answer: According to our best recollection and records, the Pharmaceutical Manufacturers Association has never provided funds to The National Alliance of Senior Citizens for any such purpose.

6. Question: "In the last 3 years, has the PMA provided funds to any of the following: The Center for Drug Development; Dr. Louis Lasagna; Medicine in the Public Interest; Medical Tribune; Pharmacists Planning Service, Inc.; Fred S. Mayer; or The Asthma and Allergy Foundation? If so, for what purposes were these funds provided and in what amount?"

Answer: On October 24, 1986, the Pharmaceutical Manufacturers PMA commissioned a study by the Center for Drug Development at Tufts University, headed by Dr. Louis Lasagna, on "Implementation of the Drug Price Competition and Patent Term Restoration Act of 1984: A Report on the First Two Years." The amount paid for the study was \$5,000.

In each of the past two years, PMA has contributed \$500 to Pharmacists Planning Service, Inc. as a general membership fee.

PMA has not provided any funds to any of the others listed above in the last three years.

7. Question: "According to testimony given by Dr. Goyan and Dr. Young, bioequivalency can vary from lot to lot of the same brand drug. Do you agree? If so, could switching from lot to lot of the same drug pose the same medical problems that according to your testimony, can result from switching from a name brand to an FDA "A" rated generic substitute?"

Answer: For the same drug manufactured by the same manufacturer, brandname or generic, bioequivalence testing is not routinely used to assure quality control as that term is used by the Food and Drug Administration. Instead, to assure lot-to-lot consistency, the FDA and pharmaceutical manufacturers rely on validated drug-production processes operated in accordance with Current Good Manufacturing Practices (CGMP). We know of no evidence of clinical bioinequivalence resulting from lot-to-lot variations where manufacturers have used such a validated drug-production process in accordance with CGMP.

Both FDA and the Pharmaceutical Manufacturers Association long ago recognized the inadequacy of end-product testing as a measure of product quality and have worked together to develop "process validation" to assure uniform quality of drug products within lots and from lot to lot. In vitro methods and analytical assays are used to assure that the manufacturing process remains within designated control limits and that products meet regulatory specifications.

The problem is not lot-to-lot variation of brandname drugs. Problems arise because the current system for determining therapeutic equivalence of different products through bioequivalence testing is inadequate to assure safety and efficacy under all expected conditions of use. This is demonstrated by the case histories discussed by PMA President Gerald J. Mossinghoff on October 21, 1987 and set forth in the Appendix to his testimony.

8. Question: "Does the PMA have any estimate of what market share it has lost to generic drugs since January 1, 1985? Does it have any projections for what share of the market generics will control in the next 5 years? If so, please provide those figures to the Subcommittee."

Answer: The Pharmaceutical Manufacturers Association does not have any estimate of the market share its members have lost to generic drugs since January 1, 1985. However, according to Arthur D. Little Inc., sales of generic drugs now represent about 25 percent of all prescription-drug sales. By 1991, Arthur D. Little projects sales of generic products will represent about one-third of all prescription-drug sales. Typically, when the patent on a brandname drug expires, the innovator company will lose about 30 percent to 40 percent of prescriptions dispensed to generic versions of the drug. Some of the generic versions are made by PMA member companies, but their share of the generic market is declining. In 1984, according to IMS America data, PMA member companies accounted for 72 percent of the dollar volume in sales of generic versions of pioneer products. By 1986, IMS data show this figure had fallen to 56 percent.

Senator METZENBAUM. We will now hear from Dr. Frank Young, who has very patiently waited during this entire period. If you care to bring somebody to the table with you, I do want to say that I think it speaks very well for Dr. Young that he was willing to be this patient.

Our usual procedure is to take a government witness first, but in this instance I think it served an important purpose for him to be able to hear some of these other witnesses, particularly the PMA. We are happy to have you with us.

After we hear from Dr. Young, we will conclude our hearing by hearing from the AARP, whose testimony we certainly do want to hear.

Dr. Young, please proceed.

STATEMENT OF FRANK E. YOUNG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES, WASHINGTON, DC

Dr. YOUNG. Mr. Chairman, if I could, I would like to summarize the points in my statement and then I will be delighted to respond to questions. I have one chart that I would like to use to illustrate the bioequivalency standard, if I might, during the testimony.

Senator METZENBAUM. Please do; please proceed.

Dr. YOUNG. The most important points that I would like to make are as follows. First, I cannot stress more strongly that the future good of the generic industry and the health and the well-being of the American population depends upon the strength of the innovator companies within the United States.

It is those companies that make the broad discoveries that are required to introduce new pharmaceutical agents and, as the U.S. representative to the Executive Board of the World Health Organization, I know firsthand that many countries look to the United States for the development of many of these new drugs.

Our ability to approve generic drugs is based on our confidence that the same approval process, as mentioned earlier today, is able to deal with approvals of new innovative drugs. We use essentially the same criteria for approval of both innovative drug and generic versions of those drugs.

We are dedicated at FDA to fostering the environment that will be conducive to the continued productivity of the pharmaceutical research and development industry, leading to major therapeutic advances.

For example, we can accomplish this goal by enhancing the quality and the timeliness of the new drug approval process. We all recognize that marketing of a new drug generally occurs after years of intensive research and expenditure of millions of dollars by the innovator.

I would also like to point out that for every 2,000 ideas that are explored in the laboratory, only one of these reaches the market, a point that was discussed substantially, and we are trying to deal with the regulatory burden through revising our regulations, developing new guidelines, and augmenting our staff. It has been a long-avowed goal to reduce the time for new drug evaluation.

The 1984 law mandated for all generic drugs an abbreviated application procedure which does not require the sponsor to repeat the costly, time-consuming safety and effectiveness studies that were already conducted by the pioneer.

Instead, the sponsor must show that that product is bioequivalent to the pioneer product and that the drug will be manufactured in accordance with the same high standards. Since that time, I am pleased with the work that has been done in our generic drug evaluation office, as well as that done in the evaluation of new innovative drugs.

Nevertheless, we have heard some criticisms. The first criticism deals with the way in which bioequivalency studies are undertaken and, if I could please have the chart displayed, I will be able to provide some, I think, clarification for this.

This is the observed differences in mean area under the drug concentration time curve, and it displays the percent of difference of the mean area under the curve for the generic versus brand name drug.

You will note that the levels that we have been speaking about are plus or minus 20 percent. These are statistical issues. These are not issues of variability in each individual case.

For example, in the graph, you will see that the vast majority are around plus or minus 3 percent and very few are beyond 10 percent. And, in fact, it would be unlikely, as I have stated in my testimony, that FDA would approve something beyond the plus or minus 20 percent level.

Well, what is the meaning of a plus or minus 20 percent here? It is adjudged in chemical tests that the best chemical precision is plus or minus 5 percent, and as I have pointed out in my testimony, the USP for chemical tests of individual tablets or capsules uses a plus or minus 15 percent.

In biological tests, in contrast, a plus or minus 10 to 15 percent is usual. For example, if you or I were to do a serial dilution, a serial tenfold dilution on a known number of bacteria and plate them on petri dishes and do it with the most impeccable care that we could, it would be unlikely that all of our results would be closer than plus or minus 10 to 15 percent. That is a biological error that occurs.

Thus, we have adopted with that same level of conservativeness a plus or minus 20 percent on mean values, and this is on a statistical basis. I must also hasten to point out that this is the exact same standard that is used when a brand name drug lot is manufactured at different sites or in lot-to-lot variation.

We expect a plus or minus 20 percent to occur, whether it be in the approval of a generic drug or the approval of a new version of a brand name drug.

Senator METZENBAUM. Dr. Young, may I just interrupt you for a minute? As I look at the chart, is it not the fact that the overwhelming number of variations are within the plus or minus three percent, that a very substantial portion are within the plus or minus 10 percent, and that only one gets up to 19 on the plus side and on the minus side only one gets up as far as about 14? Now, am I misinterpreting the chart?

Dr. YOUNG. No. You are absolutely correct.

Senator METZENBAUM. So that the plus or minus 20 is the standard, but the reality is that most of them are far, far less than the 20 percent?

Dr. YOUNG. That is absolutely correct, and that is a key point and it is the same standard that is used in the approval of brand name drugs from lot to lot as it is in generic drug approval.

That is why I stated that it would be very unlikely that FDA would go toward the margins of that plus or minus 20 percent; in fact, I believe the one that you said was at the end of the plus side was an older action. So, you are absolutely correct.

[The following material was subsequently supplied for the record:]

5.

Information on the one drug that was high on the plus side of the chart displaying observed differences in mean area under the drug concentration time curve.

Response: The one drug product referenced in Dr. Young's testimony that was on the high side of the chart that he used at the hearing was a 40 mg. propranolol tablet manufactured by Mylan Laboratories. This was one of the first propranolol applications approved by FDA.

The in vivo bioavailability/bioequivalence study was a steady state three-way crossover comparing Mylan's 40 mg. propranolol tablet with Ayerst's 40 mg. Inderal tablet and a propranolol solution.

The study was done at the Morgantown Medical Arts Building under the direction of Thomas S. Clark, M.D. The plasma samples were analyzed by J. P. O'Donnell, Ph.D. at the West Virginia School of Pharmacy.

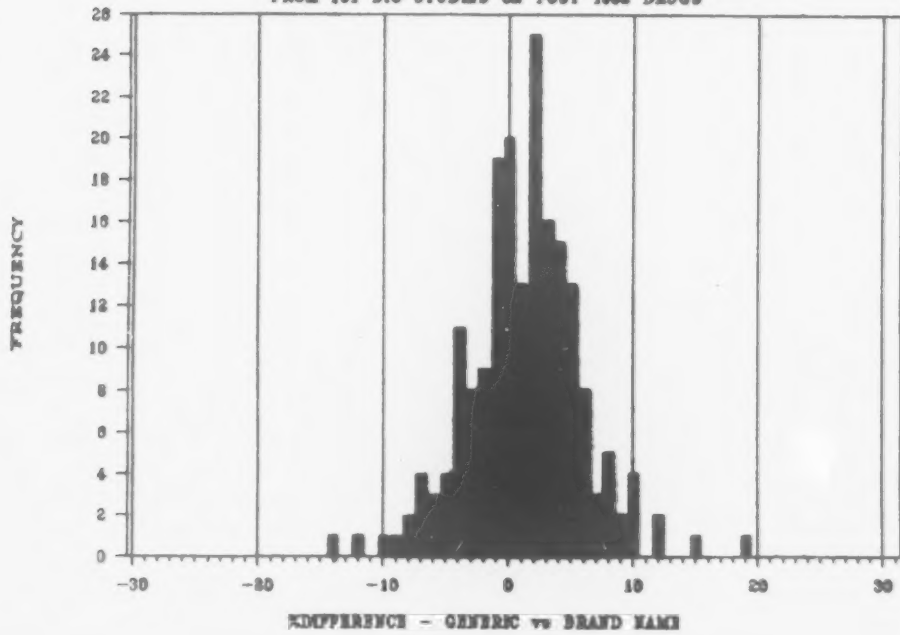
Propranolol is a drug that is rapidly metabolized on its first transit through the liver (first pass effect). Thus, the amount of propranolol in the blood is small compared to its metabolites. The observed differences in the mean area under the curve (AUC) shown on the chart, about 19 percent higher for the Mylan product than the AUC for the brand name product, represents only the propranolol level. The difference between the two products in the AUC for propranolol and its metabolites is about 10 percent.

Although evaluation methods have changed slightly since this study was approved, the FDA has no reason to believe that the Mylan product is not bioequivalent to the Ayerst Inderal product.

Attachment

fig. 1: Observed AUC Differences

FROM 191 BIO STUDIES ON POST 1982 DRUGS



Senator METZENBAUM. That is the only one that is up there and the next one is a single one again at around 14 percent-plus. So you really only have three up over 10 percent in the plus side, and actually about 3 on the minus side.

Dr. YOUNG. Yes, and in studies we have reviewed, the average variation in blood levels between the pioneer drugs and the generic drugs is actually only around 3½ percent, which is small compared to the variables inherent in drug therapy.

Senator METZENBAUM. In view of the fact that it appears it would make very little difference, as I understand the PMA, it seemed they were talking about making the variation a plus or minus 20 or something less than that. Is that something worth considering, because it would appear that if you made it plus or minus 15, it would practically have no effect, and if you made it plus or minus 10, it would have almost no effect, very little effect?

Dr. YOUNG. I have already addressed that question to our staff as part of the evaluation of the transcript of the hearing on bioequivalency that FDA held for about three days. As part of this, we will now prepare a report, and one of the things that we are going to look at is that percent difference, and it clearly could be narrowed. I do not think that is a significant issue of safety at all, based on what is there. We would be delighted to communicate to you, to the Administration, academe and industry exactly what we find. We are in the process of evaluating that now.

Senator METZENBAUM. Please proceed.

Dr. YOUNG. The other major criticism that has been raised about bioequivalence deals with the validity of using young and healthy volunteers as subjects for bioequivalency studies.

According to this argument, sick patients can be expected to absorb and metabolize a drug differently than do young, healthy volunteers. Therefore, according to this argument, bioequivalency testing is not an indicator of how the drug will actually perform in sick patients.

I should point out, however, that these are the same tests that are performed on pioneer drugs before their final forms are marketed. Again, we have tried to keep symmetry between the pioneer and the generic drugs.

Another broad area of concern is as follows: generic drugs cause harm. For each claim of this type that has come to our attention, we have made every effort to learn the details of the claim and to analyze their significance. Typically, these claims have been made at symposia or similar events through the media, but only occasionally have they been reported directly to FDA. In every case that we have studied so far, we have been able to learn the details and we have found that the initial reports were substantially in error in some way or another. When we have asked for details, we have not always been successful in getting a response. Nevertheless, we have investigated such claims in the past and we shall investigate such claims in the future.

I can fully verify the statement that you made that we had looked into the case in the Cleveland Clinic. We are getting the records. Additionally, they have been very cooperative. We will determine whether or not there are other generic versions of the brand name drug used and whether there were clinical responses.

But as we searched our files, we found that there were 12 adverse reactions reported for the brand name drug and three by generic versions. So, therefore, in any formulation of a drug there will be adverse reactions reported periodically. This is not unexpected.

In fact, I would submit that if we tried to approve only drugs that were one hundred percent failsafe, FDA would never approve a single drug, and we get criticized just a little bit every once in a while for being a bit tardy, as it is.

So we couple post-market surveillance with a pre-market approval system. One cannot look at one separate from the other, and as we have looked at these post-market concerns over generic drugs, we have not found problems that we could document.

We are very open to receiving these claims of harm, and I really welcome the opportunity to provide information on the cases raised by PMA, and any others that come forward.

I have put forward personally a call for any reports of problems in bioequivalency, and as I was correctly quoted in this hearing, very little scientific, new information came forward.

Senator METZENBAUM. Dr. Young, we have been notified that there will be a roll call shortly, so if we could ask you to wind up as quickly as you can.

Dr. YOUNG. Surely. Finally, in my prepared statement I have focused on the issue of switching and will not comment further; suffice it to say, I have asked the agency to look at the "B" category of drugs in FDA's "orange" book of approved drugs. I will briefly quote for your information what we mean by the "B" category.

We evaluate as therapeutically equivalent those products that meet the following general criteria, and I will submit these criteria for the record.

[The following material was subsequently supplied for the record:]

General Criteria for Evaluating Drugs as Therapeutically Equivalent.

Response.—As stated in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book):

"FDA evaluates as therapeutically equivalent those products that meet the following general criteria: (1) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (2) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalent standard; (3) they are adequately labeled; and (4) they are manufactured in compliance with Current Good Manufacturing Practice regulations."

Dr. YOUNG. A drug that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products are those for which there are no known or suspected bioequivalence problems, or for which potential bioequivalent problems have been resolved by adequate in vivo or in vitro evidence. In the "B" group, clearly specified and clearly noted in the orange book, these are products that FDA does not at this time consider to be therapeutically equivalent to other pharmaceutically equivalent products.

This is not a midnight revelation. It is something that has been clearly stated by FDA, and one of the things that I have asked the agency to do is to now look at this "B" list, see how we can shorten

it. The "B" list is an accident in history. The law encouraging generic drug approvals occurred in 1984 and we have been implementing it. But, the "B" drugs were grandfathered. I must hasten to add there have been very few problems with these drugs, and just a suspicion of harm does not mean that harm will, in fact, occur.

Senator METZENBAUM. Perhaps the orange book ought to have a more bold-faced statement on the front cover because as I understand Mr. Mossinghoff's statement, he read it and it was on the first or second page.

Dr. YOUNG. Yes, it is, and that is a problem. We have it bold-faced there, but we can attend to other ways in which we can make that clearer.

Senator METZENBAUM. I should point out to you that although PMA does talk rather strongly about the FDA and their failure to meet certain standards that the reality is that the worst cases in recent history of adverse reactions occurred when brand name companies withheld the evidence of adverse reactions from the FDA.

I mean, it is not the cases where the FDA missed something. The worst cases that have caused injuries and in some instances deaths as well, occurred when Smith Kline and Eli Lilly with respect to various and sundry different pharmaceutical products withheld the factual data of the problems they knew existed in connection with those products from the FDA.

Where the FDA has given approval of a bioequivalent generic substitute for a brand name product, that is not where the problems have been created for the people who have ingested those drugs. And the point I want to make that the companies have created more problems in failing to share information with you than are the problems that have been created where you have had the information and acted appropriately.

Dr. YOUNG. We have had some problems with generics withholding information or coming on the market without approval, but we dealt with those just as we have with the other problems that you mentioned.

I think it is also fair to state that we would expect more problems to occur in general with brand name products in the early phases because they are just coming on stream in the market. During development of a drug about 3,000 to 5,000 patients receive the drug, but when it is marketed in the community there are millions of patients. That is why post-market surveillance is so important as part of the armament here.

Senator METZENBAUM. Thank you.

Senator Thurmond.

Senator THURMOND. Thank you very much.

Commissioner Young, we are glad to have you with us. I just have two questions. We have a vote on in seven minutes and I will see if we can dispose of them real quickly.

Does the FDA have authority to deal with all instances of unfair or anticompetitive activity directed at the generic industry?

Dr. YOUNG. Let me ask counsel to reply to that, as that is a legal question.

Mr. SCARLETT. We have the authority to govern the content of prescription drug advertising and of drug labeling generally. To the extent that anticompetitive activity generates false or misleading advertising or labeling, FDA has the authority to act.

However, if that type of effect is not present, the FDA does not have the authority to deal with anticompetitive practices and we leave that to the Department of Justice.

Senator THURMOND. In those instances in which you do have authority, are you able to adequately deal with the problem, and do you obtain compliance from the offending entities?

Mr. SCARLETT. My impression is that we have adequate authority and that the agency staff does an excellent job of regulating this aspect of the drug industry. Dr. Young or Dr. Rheinstein could elaborate on that.

Dr. YOUNG. Yes, I would certainly concur that we have been able to move rather swiftly where problems exist. But, again, it is important to emphasize that we have to get the evidence and not act on flimsy allegations. Where we have, we have moved rapidly and I have been pleased with the action that the agency has been able to take.

Senator THURMOND. Thank you. Commissioner Young, I notice you have on a uniform.

Dr. YOUNG. Yes, sir.

Senator THURMOND. What does that represent?

Dr. YOUNG. This is a U.S. Public Health Service uniform and I am very proud to wear this. I have looked at my career in Washington as a call to duty. I joined the Corps when I came here and have been a very strong proponent of public service, and I am delighted to be here in such a capacity.

Senator THURMOND. Are the commissioners always selected from the Public Health Service or were you selected outside, or would have been selected outside, maybe?

Dr. YOUNG. I came from outside. I was dean of the School of Medicine and Dentistry at the University of Rochester and vice president for health affairs, and I had the responsibility of overseeing approximately 6,000 employees and faculty in five different hospitals.

Senator THURMOND. You are still an officer in the Public Health Service?

Dr. YOUNG. Pardon me?

Senator THURMOND. You are still an officer in the Public Health Service?

Dr. YOUNG. Yes, sir.

Senator THURMOND. Thank you very much.

Dr. YOUNG. Thank you, Senator.

Senator METZENBAUM. Senator Specter.

Senator SPECTER. Thank you very much, Mr. Chairman.

I regret that I could not attend all of the hearings. I was here earlier, and we are debating the War Powers Act on the floor and I have been there until just a few moments ago, but I do have a few questions of Dr. Young.

Dr. YOUNG. Yes, sir.

Senator SPECTER. Senator Thurmond reminds me that we vote in 5 minutes, and I will try to stay within 5 minutes.

Dr. YOUNG. And I will answer very rapidly, sir.

Senator METZENBAUM. And we have the AARP, who has not been heard from yet.

Senator THURMOND. We have one more witness, too.

Senator METZENBAUM. They have 1,280,000 members in Pennsylvania.

Senator THURMOND. Short questions and short answers. [Laughter.]

Senator SPECTER. I will still try to stay within 5 minutes.

Dr. YOUNG. Yes, sir. [Laughter.]

Senator SPECTER. Commissioner Young, what is involved in grand total in terms of savings to the consumer if there is widespread availability of generic drugs?

Dr. YOUNG. I cannot give you the absolute figure. I will provide that for the record. The subcommittee's chart of examples clearly shows that there are substantial savings on drugs that are already off patent and are well known to be safe and effective.

Senator SPECTER. I would be interested in as much precision as you can provide on that point.

Dr. YOUNG. I will provide that for you, sir.

[The following material was subsequently supplied for the record:]

What is involved in grand total in terms of savings to the consumer if there is widespread availability of generic drugs.

Response.—The Food and Drug Administration does not monitor the savings that can accrue to the consumer if the physician authorizes substitution and the pharmacist chooses to practice drug product selection. However, we are aware of studies in this economic area. For example, based on the information in one commercial source's data base, the American consumer would have saved \$404,752,000 in 1986 due to the prescribing and dispensing of generic drugs in community pharmacies in the United States. A report by the Federal Trade Commission, "Generic Substitution and Prescription Drug Prices 1985," estimated that the savings to the consumer in 1984 due to drug product selection was between \$130 million to \$236 million. The National Center For Health Services Research And Health Care Technology Assessment wrote a report entitled, "Generic Drug Laws; A Decade of Trial—A Prescription for Progress June 1986" in which they quote an estimate of the generic market at about 4.5 billion annually.

Senator SPECTER. What is your judgment as to the extent that the broadest availability of generic drugs would discourage research and development by the brand name producers?

Dr. YOUNG. I will answer your question rapidly and provide more information for the record, if I can. We have to keep a very balanced approach. We must foster, clearly, the development of innovator products. We can do this in two broad ways, and FDA is working on both of them.

One, we can look at what are the problems involved in clinical trials and cut down false starts. We have reviewed in excess of 620 new drug applications since 1980 and we have found a number of false starts, i.e., investigations that could not be used in the evaluation process. We want to hone in on that problem and see what can be done to sharpen up the total drug evaluation process, not to make it less effective, not to take shortcuts, but to provide also the best possible guidance during the exploration.

The second thing that must be done is to expedite and improve the quality of the drug approval process because it takes too long. Those things have to be done to put into effect the stimulation for

the innovator. It is not fair for the innovator to be held captive either scientifically or bureaucratically for long periods of time.

On the other hand, it is similarly not fair, once we provide the appropriate patent protection and market return, to not bring on to the market, as Congress has willed, those drugs that meet fully the Hatch-Waxman provisions of generic drugs, because that law both extended patents and provided for competition. We must be fair in implementing both parts of it.

Senator SPECTER. Commissioner, did you hear my questioning of Dr. Goyan earlier this morning?

Dr. YOUNG. Yes, I did, sir.

Senator SPECTER. I would be interested in your judgment as to the substitution factor. Is it realistic to substitute freely a generic drug for a brand name without any realistic or significant risk to the patient?

Dr. YOUNG. I tried to clearly address that in the last portion of my testimony, and due to the four minutes or three minutes you have now, I will answer very rapidly. There are two types of generic drugs, those that are in the "A" category and those that are in the "B".

We would not state, and did not state in the orange book, that we have absolute equivalence on those that are in the "B" group. I might also add that we have had a situation where two brand name products were approved for the same chemical entity through full new drug applications, and we would not advocate substitution there.

In the vast majority, when FDA has said they are equivalent, we fully believe that they are equivalent and can be substituted. As a physician, I would say there may be a small group—this is what Dr. Goyan spoke to—of clearly less than 5 to 10 percent of the patients that may be titrated ever so closely that it would not be appropriate to either switch from a generic to a brand or a brand to a generic.

In all cases, in my opinion, the physician is the person that we hold responsible in society for our care, and in that sense I support the comments that were made earlier that the physician must have the ability to control this as long as our system holds the physician responsible.

But it is a small number. In the vast majority of cases, there are no problems at all; there may be some individual variabilities and there we have to rely on the physician's judgment.

Senator SPECTER. Dr. Goyan put the figure at five percent. Do you think it is in the 5- to 10-percent range?

Dr. YOUNG. I would not have the figures, but from my previous experience in academic medicine I would not put it above 10 and I have no problem with 5 percent.

Senator SPECTER. But you think the switch from brand to generic or vice versa ought to be accomplished only with a physician's prescription as opposed to a layman making the change himself or herself?

Dr. YOUNG. I think that it has to focus on the particular case involved.

Senator SPECTER. And you need medical advice to make the change?

Dr. YOUNG. You need medical advice in that 5 to 10 percent, and I have got to keep focusing on that 5 to 10 percent. In the vast majority of cases, no problem, and I do not want my comments in any way to be interpreted as putting up a barrier on the use of generic drugs.

Senator SPECTER. And a final question—you may want to refer this to your lawyer—does your agency have the authority to deal with the problem where physicians may be improperly motivated by free airplane tickets to prescribe one drug or another?

Dr. YOUNG. Let me refer that to counsel.

Mr. SCARLETT. I do not think that FDA is in the position to deal with the motivation of physicians. Promotional offerings—

Senator SPECTER. You do not have the jurisdiction over promotional matters?

Mr. SCARLETT. We do have jurisdiction over promotional matters to the extent that they constitute false and misleading drug labeling or are inconsistent with our prescription drug advertising regulations. Whether a particular promotion would fall into that category is impossible to say in the abstract.

It sounds to me as if the activity complained of does not involve representations about the drug. It is simply a type of promotion that is objectionable for reasons related to matters over which the FDA does not have regulatory jurisdiction, and I think that is about as much as I could say in the absence of a specific case.

Senator SPECTER. Well, I would appreciate it if you would take a closer look at that. I do not know the scope of your jurisdiction. Dr. Goyan made a comment about it being a kickback. I am not sure that it is.

Mr. SCARLETT. You are concerned specifically about the—

Senator SPECTER. Excuse me. There may be an aspect of commercial bribery in it in terms of an inducement that is inappropriate for a professional judgment. But I would be interested to know whether your agency has any authority to reach that kind of a practice.

Mr. SCARLETT. And you are concerned with, for example, the frequent flyer type of promotion?

Senator SPECTER. Well, that is the example which was brought up.

Mr. SCARLETT. OK, yes.

Senator SPECTER. Or any similar types of promotional activity where the judgment of the physician is inappropriately influenced by some pecuniary gain to himself as opposed to an objective determination as to what kind of medicine ought to be prescribed.

Senator THURMOND. Any type of inducement, I presume, Senator.

Senator SPECTER. Yes.

Senator THURMOND. Any type of inducement.

Dr. YOUNG. We will definitely provide that for the record.

[The following material was subsequently supplied for the record:]

Does FDA have any authority to deal with promotional inducements to the physician to prescribe certain drugs.

Response.—At the hearing, Senator Specter asked whether FDA has “. . . authority to deal with the problem where physicians may be improperly motivated by free airline tickets to include “. . . any similar types of promotional activity where the

judgment of the physician is inappropriately influenced by some pecuniary gain to himself as opposed to an objective determination as to what kind of medicine ought to be prescribed."

I responded that the Agency has jurisdiction over promotional matters to the extent that they constitute false and misleading drug labeling or are inconsistent with the Agency's prescription drug advertising regulations. I said I would examine the matter further and provide a follow-up for the record.

I have obtained what information the agency appears to have about these inducement programs. The Ayerst program for Inderal LA offers a chance of airline tickets or medical equipment in exchange for filling out patient profile reports. Burroughs-Wellcome has a point system in which qualified participants receive points for using boxes of three drugs: Anectine Injection, Tracrium Ampules, and Tracrium Multi-Dose Vials. Participants, limited to anesthesiologists and certified registered nurse anesthetists, may select from a catalogue of medical instruments for which various point amounts are required. Awards (medical instruments) are issued to departments of anesthesia.

The promotional materials distributed in connection with those programs qualify as drug labeling, which is defined in § 201(m) of the Food and Drug Act, 21 U.S.C. 321(m), to mean all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article. The phrase "accompanying such article" has been interpreted broadly. There is no requirement of physical accompaniment. It is sufficient that the material state or imply the intended use of the product. See, e.g., *Kordel v. United States*, 335 U.S. 345, 350 (1948).

However, for any labeling to violate the Act the labeling must cause a product to be misbranded. The misbranding provisions of the Act provide, in relevant part, that a drug is deemed misbranded if its labeling is false or misleading in any particular. Section 502(a), 21 U.S.C. 352(a). The practices at issue encourage physicians to select one among several products approved for the same indication. The promotional materials do not, however, appear directly or indirectly to convey information about the product, or about competitive products, and therefore they are not false or misleading.

In sum, whether or not the practices are objectionable, they are the kind of promotional activities Congress has included within FDA's jurisdiction.

Dr. YOUNG. I want you to know that the time that I served as dean, we clearly admonished our physicians that that type of succumbing to inducements was not appropriate.

Senator SPECTER. Do you have more or less power as Commissioner than you had as dean?

Dr. YOUNG. I think I have much more, and enjoy it much more.

Senator METZENBAUM. I might say to my colleagues that Mr. Mossinghoff indicated a personal disapproval of that type of practice, and I asked him if he would put that on the agenda of the PMA's board meeting to discuss the possibility of declaring that kind of conduct unethical and inappropriate.

Also, if that response is not adequate, I intend to ask the FTC to inquire on the subject, and we welcome both of you joining in that request, but are not ready to do that at the moment.

Thank you very much. Dr. Young, I am going to ask you some questions very briefly; I would hope you could answer them very briefly.

Dr. YOUNG. I hear your time constraint. I shall try to make it in 30 seconds or less.

Senator METZENBAUM. On the 1,000 drugs mentioned by the PMA, am I correct that FDA does not allow unsafe drugs on the market?

Dr. YOUNG. That is correct.

Senator METZENBAUM. Have you received any significant increase in reports of problems with the FDA-approved generic equivalents since they have been on the market?

Dr. YOUNG. To the best of my knowledge, no. Peter, have you had any information?

Dr. RHEINSTEIN. No.

Dr. YOUNG. No, not to the best of our knowledge.

Senator METZENBAUM. Are there more recalls of FDA-approved generic drugs than of name brands?

Dr. YOUNG. I do not believe so. We will provide that information for the record.

[The following material was subsequently supplied for the record:]

Are there more recalls of FDA-approved generic drugs than of name brands.

Response.—A comprehensive report published in April 1980 by the FDA's Office of Planning and Evaluation, "An Analysis of Prescription Drug Recall Rate," OPE Study 52, concluded that based on sales data, only 0.42 percent of multisource, therapeutically equivalent drug products were recalled because of a defect posing a potential health hazard (Class I or Class II recalls). This percentage of recalls based on sales of therapeutically equivalent multisource-products is small and not substantially different between generic and brand name drug products. Thus, FDA could not support a contention by a large research oriented drug company that brand name products had superior quality as measured by recall rates compared to those for generic drug products.

Senator METZENBAUM. Do you feel that, generally speaking, generic drugs are safe?

Dr. YOUNG. Yes.

Senator METZENBAUM. Are generic drugs subject to the same FDA standards for manufacture and quality control, and are they inspected in the same way?

Dr. YOUNG. We provide the same type of inspection for both brand names and generics.

Senator METZENBAUM. Thank you very much. We may have a couple of additional questions to submit to you, but I do appreciate very much your cooperation. Thank you very much.

Dr. YOUNG. Thank you.

[Statement and response to questions follow:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY
FRANK E. YOUNG, M.D., Ph.D.
COMMISSIONER
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON ANTITRUST, MONOPOLIES,
AND BUSINESS RIGHTS
COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

OCTOBER 21, 1987

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I am happy to honor your request to testify today about the safety and efficacy of generic drugs approved by the Food and Drug Administration (FDA) and the status of our generic drug review program. I am proud of our record in implementing the initiative of the landmark Drug Price Competition and Patent Term Restoration Act of 1984, which both stimulates innovation through patent extension and fosters competition through encouraging development of safe and effective generic drugs for the marketplace.

I cannot stress enough that the future good health of the burgeoning generic drug industry in this country -- not to mention the public health generally -- depends upon the U.S. pharmaceutical industry remaining a world leader in innovation, developing important new drugs for the medical profession and the public. I know from my experience as the U.S. representative to the Executive Board of the World Health Organization that other countries look to the United States for new ideas. For example, our pharmaceutical industry has been in the forefront of the revolution in biotechnology, creating products that hold the promise of revolutionizing the practice of medicine.

Our ability to approve a generic drug with confidence is based in large measure on the therapeutic quality of the innovator's drug. As you know, the abbreviated approval process that is now in place for all generic drugs is based on the assumption that the innovator's product works and works well. Thus the generic manufacturer must be able to demonstrate an equivalence to the innovator's product.

We at FDA are dedicated to fostering an environment conducive to the continued productivity of pharmaceutical research and development leading to major therapeutic advances. We can accomplish this goal by enhancing the quality and timeliness of the new drug evaluation process. We all recognize that the marketing of a new drug entity generally occurs only after years of intensive research and expenditure of millions of dollars by an innovator firm to develop a new product, including the costs of many failures. In fact, for every 2,000 ideas that are explored in the laboratory only one results in a marketed drug. We are working to minimize the Federal regulatory burden through revised regulations, guidelines and administrative improvements, including our augmented review staff, to reduce the time required for new drug review.

We are also keenly interested in assuring that our premarket review for generic versions of these drugs remains scientifically sound and efficiently run. As we all know, the 1984 law mandated for all generic drugs an abbreviated application procedure which does not require a sponsor to repeat costly and time-consuming safety and effectiveness studies already conducted by the pioneer. Pather, a sponsor must show that the product is bioequivalent to the pioneer product and that the drug will be manufactured in accordance with our same high standards.

The productivity and accomplishments of FDA's generic drug review team, consisting of the Division of Generic Drugs and the Division of Bioequivalence, have surpassed all our expectations. During the past 12 months, 660 abbreviated new drug applications (ANDAs) have been approved, most of them for generic versions of post-1962 drugs. By comparison, before

enactment of the 1984 law, the average approval rate was approximately 350 ANDAs annually.

Not only are we pleased with the quantity of generic drug approvals, but we are also confident that the quality of data in applications that have received approval reflects the current technology in the sciences of biopharmaceutics and drug product production. For example, approvals of generic versions of post-1962 drugs in solid oral dosage forms are based on human studies to determine bioequivalence with their brand name counterparts, while most pre-1962 generics were approved on the basis of in vitro, or "test tube," data only.

Criticisms of Generic Drugs and FDA's Processes

Because of the dramatic impact of the new law on the pharmaceutical marketplace, interest in the quality and equivalence of generic drugs has intensified in the last three years. Obviously, we at FDA do not have any preference for generic drugs over brand-name drugs, or vice versa, but we are concerned about questions that have been raised about the safety and effectiveness of generic drugs as they might reflect upon the scientific validity of the drug review process that allows these drugs to be legally marketed.

We have regarded such criticism as an opportunity to reexamine our standards and processes. Over the past three years we have devoted considerable effort to making sure that the quality safeguards provided through our ANDA review procedures and policies as they now exist are fully

understood and to reexamining our policies with a view toward their improvement and adjustment if good science and sound regulatory practice would be better served.

Two primary issues were identified: (1) criticisms of our review criteria for bioequivalence, and (2) claims of actual harm alleged to have occurred to patients as a result of their having taken generic drugs. I would like to address both briefly.

Bioequivalence

Criticisms of our review criteria for bioequivalence have involved a number of arguments that we have evaluated with considerable interest and introspection. After carefully reviewing our answers for each criticism, I am satisfied that our review procedures for generic drugs are scientifically sound.

In trying to assess the validity of the arguments in the debate over what are appropriate standards for variation of generic and brand-name products, it is important to keep a sense of perspective. We should view bioequivalence in the context of other variables inherent in drug therapy.

For example, most chemical tests are reliable to within a 5 percent range. Even so, official standards set by the United States Pharmacopeia, an independent standard setting organization, permits a plus or minus 10 percent variation in potency for most drugs, and a plus or minus 15 percent variation for individual tablets or capsules. These standards include

pioneer as well as generic drugs. Most biological tests are even less reliable than are chemical tests. A variation of plus or minus 15 percent is considered good for many such tests. We should also bear in mind that there are many other variables in drug therapy. For example, drug dosages tend to be standardized for all patients rather than titrated, that is, specifically adjusted, for most drugs. Thus, the same 250 mg dose of an antibiotic may be given to a 100-pound female patient and a 200-pound male.

Stated simply, FDA's review of generic drugs is based on a longstanding requirement that a generic solid oral dosage drug product must be shown to have a rate and extent of absorption that, from a statistical standpoint, will not differ from an innovator's product by more than 20 percent.

This "plus or minus 20 percent rule" is a statistical one that refers to a level of confidence we must have that the average difference in rate and extent of absorption between a pioneer and a generic drug will not likely be more than plus or minus 20 percent among the patients who will take the generic drug nationwide. In order to have this statistical confidence, we generally will not approve products based on studies that show an average difference that even approaches a 20 percent difference.

However, even at its outermost boundary of 20 percent, we are confident that, with very few exceptions, the variability permitted by our requirement would not affect therapeutic outcomes. Nonetheless, arguments have been presented which are critical of the amount of variation that our "plus or minus 20 percent rule" allegedly allows in the bioavailability of generic

drugs. However, these arguments tend to be hypothetical and refer to situations that have, to our knowledge, never occurred and that, in our view, are not likely to occur.

For example, one argument is that because of the possibility of a variation of plus or minus 20 percent in the blood levels between the brand-name and the generic products, generics may differ by as much as 40 percent from each other. In reality, in studies we have reviewed, the average variation in blood levels between pioneer drugs and generic drugs is actually only around 3.5 percent, which is small compared to other variables inherent in drug therapy. As I stated earlier, a generic drug would not be approved if the average variation between it and the brand-name product were plus or minus 20 percent in bioequivalence tests. Average deviations of more than 10 percent between generic and brand-name products have been rare. The attached chart shows the observed differences between the generic drugs approved in the first two years after the 1984 legislation and their brand-name counterparts.

Another argument critical of FDA's position that has been expressed about bioequivalence involves the validity of using young, healthy volunteers as subjects for bioequivalence studies. According to this argument, sick patients can be expected to absorb and metabolize the drug differently than do the young, healthy volunteers. Therefore, according to the argument, bioequivalence testing is not an indicator of how the drug will actually perform in sick patients. I should point out, however, that these same tests are performed for pioneer drugs before their final dosage forms are marketed.

It is true that the same drug may perform differently in young, healthy volunteers as opposed to sick patients. But we have seen no convincing data to support the hypothesis that two products found by conventional tests in healthy normal subjects to be bioequivalent will behave differently from one another in patients. Moreover, there are ethical and practical reasons for testing drugs in healthy volunteers. I am sure we would all agree that it is preferable to subject healthy people, rather than already weakened patients, to the blood sampling and other discomforts of bioequivalence testing. Further, sick patients are usually on several medications simultaneously, confounding the analytical process and increasing variability of results. Therefore, we continue to believe that it is more appropriate to determine bioequivalence based upon testing in healthy volunteers than in patients.

Time concerns prevent me from reviewing every bioequivalence argument we have heard in recent years. But it is worth mentioning that FDA conducted, and I presided over, a three-day public hearing on bioequivalence last fall in an effort to air all of the issues related to this subject and to provide all interested parties an opportunity to comment. The hearing drew over 50 speakers and an audience of more than 800 scientists, lawyers, drug manufacturers, and other interested people from this country and from abroad. The published transcript is over 750 pages. We have analyzed the transcript and the comments submitted to a public docket we established for that purpose.

A task group I appointed will report to me in the near future with its report. That report will address material submitted to FDA after the

hearing concluded as well as during the three days of the hearing. Our first impression, however, was that data were lacking to support the criticisms that we heard. By the end of the hearing, I found the lack of data noteworthy.

As I said, however, some material was submitted after the hearing ended. We have reviewed that material with an open mind and are committed to remaining open-minded should something new come to our attention that is supported by credible data.

Claims of Harm

The second broad area of criticism involves claims that approved generic drugs have caused actual harm. For each claim of this type that has come to our attention, we have made every effort to learn the details of the claim and to analyze their significance. Typically, these claims have been made at symposia, or similar events, or through the media, but only occasionally have they been reported directly to FDA.

In every case where we have been able to learn the details, we have found that the initial reports were in substantial error in some way or another. When we have asked for details, we have not always been successful in getting a response. Nevertheless, we investigate such claims and we are not averse to changing our procedures if that is warranted.

At our bioequivalence hearing, for example, a few physicians spoke of patients who suffered serious adverse effects from generic drugs. We asked them to give us details so that we could investigate. They did not do so at the time, and when we sent them letters again asking for more

facts, they did not respond. We have yet to confirm a documented instance where a generic product has been shown to be bioequivalent after it was approved by FDA and evaluated by us as therapeutically equivalent. In that same vein, I would like to clarify FDA's position, because we have frequently been quoted out of context. We have not maintained that there has never been a single patient who did not respond to treatment with a generic drug product approved by the agency as bioequivalent. Our files contain numerous reports of therapeutic failures with both generic and brand-name products. What we have intended to say is that we have not seen a documented instance that showed a generic product that we rated as therapeutically equivalent to be, in fact, not bioequivalent.

Finally, it should be noted that problems alleged to be associated with generic drugs can also be associated with brand-name or innovator drugs. In reality, all drug products of the same chemical entity, including brand-name products, are simply different formulations of that same chemical. In our system of health care delivery, we rely on the physician to monitor any change. We are aware of a few anecdotal reports of difficulties in very sensitive patients where substitution occurred, sometimes between products rated as not equivalent by FDA. In these instances when switching products could pose a problem, it would be a problem for all versions, including brand-name versions, whether switching from a "brand-name" to a "generic" version or vice-versa. However, we can state that if a drug product is declared by FDA to be therapeutically equivalent, the physician, in managing the patient, can feel secure that authorizing substitution of that product for any other therapeutically equivalent drug will provide the same intended effect. But it is important to remember that the physician makes the

- 10 -

ultimate judgment of whether a brand-name or generic product is given based on knowledge of special needs of the patient. All State drug substitution laws recognize this by providing that the treating physician may stipulate that a particular product be dispensed.

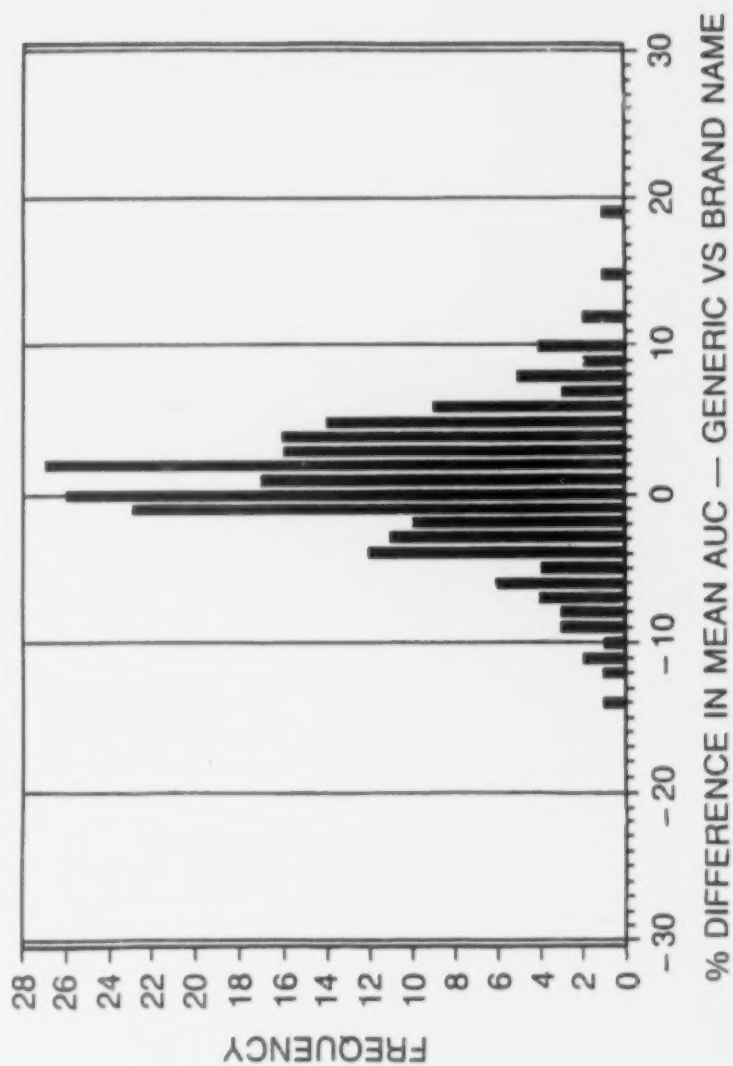
Conclusion

Mr. Chairman, I would like to reiterate how proud we are of our generic drug review program. We continue to believe that our review process for generic products is scientifically valid and that generics evaluated by FDA as therapeutically equivalent may be safely substituted for brand-name drugs.

This concludes my formal statement. I will be happy to answer any questions you may have.

OBSERVED DIFFERENCES IN MEAN AREAS
UNDER DRUG CONCENTRATION-TIME CURVE
(AUCs)

FROM 224 STUDIES ON POST 1962 DRUGS





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR 15 1988

The Honorable Howard M. Metzenbaum
Chairman, Subcommittee on Antitrust, Monopolies
and Business Rights
Committee on the Judiciary
United States Senate
Washington, D.C. 20510

Dear Senator Metzenbaum:

This is in response to your letter of November 2, 1987, to Commissioner Young, in which you asked several questions relating to the October 21, 1987, hearing on competition problems in the pharmaceutical drug industry. I regret the long delay in responding.

The questions and our responses follow:

1. Question- At the hearing, Dr. Jennings, on behalf of the PMA recommended that the FDA amend its form for tracking adverse drug reactions. Do you believe that current FDA procedures are sufficient for tracking adverse reactions that result from switching from one drug to another that is bioequivalent? Would the PMA's recommendation improve these procedures?

FDA Response- Existing regulations require that manufacturers report adverse reactions, including reports of therapeutic failure, on form 1639 or an alternative, FDA-approved format, such as form 1639a. We believe that forms 1639 and 1639a (copies enclosed) are adequate for collecting, recording, and evaluating reports of therapeutic failure of drugs, even where the drugs are switched to a generic version. The forms allow for recording patient disease and drug exposure variables, and more detailed information can be attached to them.

We have developed computerized methods to aid in processing, storing, and evaluating the information contained on forms 1639 and 1639a. Form 1639 is widely distributed (over 500,000 copies a year are mailed out) and has recently been included in the Physicians' Desk Reference (PDR). This makes the form relatively accessible.

In 1987, FDA received 1,767 reports of therapeutic failure. Approximately 90 percent of such reports are on forms 1639 or 1639a, and the drug product involved can be specifically

identified for approximately 95 percent of all reports. Item 7 of form 1639a, requests the manufacturer's name, and the instructions for form 1639 state "If a generically produced product is involved, the manufacturer should be identified." Reporters are encouraged to provide the batch number for a drug when available, especially if the report indicates lack of effect. For a cluster of reports or a well documented case, we actively try to determine the batch number.

In summary, we believe the procedures for tracking adverse reactions are adequate. Revision of the forms would be costly and would not increase the Agency's ability to track therapeutic ineffectiveness or allegations of therapeutic inequivalence.

2. Question- The PMA also testified that it had recommended to the FDA that the FDA extend a warning about the risk of switching drugs to all maintenance drugs approved through bioequivalence testing and to include such a caution in the product labeling "until such testing is scientifically demonstrated to assure safety and effectiveness." Is such a warning warranted? Would such a warning discourage the use of generic drugs?

FDA Response- We are not aware of any reason to institute the kind of warning recommended by the PMA and cited in the question. In our opinion, such a warning would discourage the use of generic drugs and would not be accurate for any generic drug product rated as therapeutically equivalent in the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluation).

3. Question- At the hearing, you suggested that perhaps 5 to 10% of all patients are so tightly controlled on medication that switching from one bioequivalent drug to another could cause an adverse reaction. Could you elaborate more on which patients fall within this range? Is there the same potential for an adverse reaction when such a patient is switched from one lot of a drug to another lot of the same drug? If a patient wants to switch from a name brand to a generic for financial reasons, can this be accomplished without harm to the patient?

FDA Response- Dr. Young's statement regarding the 5 to 10% of all patients being tightly controlled on medication is an estimate based on his own general medical background.

Page 3 - The Honorable Howard M. Metzenbaum

As to the issue of switching from one lot of a drug to another, an innovator firm in order to gain approval for a reformulated dosage form is required to perform the same kind of bioequivalence test for approval of its new formulation that a generic manufacturer would do to show equivalence to the brand name product. In our view, one would not expect to see any more clinical differences between the generic and brand name products than you would between the innovator's old and new formulations or between subsequent lots of the innovator's product.

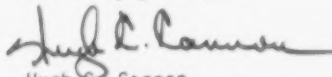
If a patient wants to switch from a name brand to a generic, this should not cause harm to the patient. There is no reason to doubt the fundamental principle that drug products delivering comparable blood levels of a therapeutic moiety in bioequivalence tests in normals will generally yield comparable therapeutic results in patients. Generic drug products approved by the Agency as bioequivalent and rated as therapeutic equivalent can be expected to yield comparable therapeutic results to the brand name counterpart they copy.

4. Question- The PMA filed an appendix with its testimony detailing cases where it contends switching from one drug to a bioequivalent drug caused problems for the patient. Please provide us with the FDA's assessment of the examples cited in the appendix.

FDA Response- Attached is a detailed analysis of each of the nine cases cited by the PMA in the appendix to their presentation. As indicated in the analysis, our Center for Drug Evaluation and Research believes that the cases cited against the bioequivalence generic drugs are not convincing. The PMA does not allege any consistent pattern of generic failure. Instead, they pick specific, largely anecdotal reports that are isolated and insignificant when compared to the wide use of generics. These cases would not cause us to revise our statements regarding the acceptability of generic drug products.

Please let us know if we can provide any further information.

Sincerely yours,



Hugh E. Cannon
Associate Commissioner
for Legislative Affairs

3 Enclosures

ANALYSIS OF NINE CASE REPORTS
IN PMA TESTIMONY OCTOBER 21, 1987
BEFORE SENATE SUBCOMMITTEE

The following represents an analysis by the Office of Drug Standards in the Center for Drug Evaluation and Research of the documentation provided by the PMA in its testimony before the Senate Subcommittee on Antitrust, Monopolies and Business Rights of the Committee on the Judiciary October 21, 1987.

Case Report 1 (1987) - Primidone

This report was published in the JAMA of September 4, 1987. Although the article failed to state when the incident occurred, subsequent FDA investigations found that it was in the fall of 1985 that patient in Cleveland Clinic was given generic (Bolar) for Mysoline (Ayerst). Blood levels were documented and dropped to essentially zero following the switch. The patient was 16 year old girl with congenital retardation, cerebral palsy, and she was experiencing multiple daily seizures. They had been controlled with Mysoline. She was admitted to the hospital on 10/4/85 for severe constipation. She was switched to Bolar's primidone tablets (distributed by UDL in strip packaging) in the hospital. When the patient was switched back to Mysoline, blood levels reportedly returned to normal.

It should be noted that patient was again admitted in January of 1986 for uncontrolled seizures using the Mysoline product and is now controlled with another drug.

FDA's investigation is not complete, but analysis of the suspect lot failed to show a problem, and no other problems with this product have been reported. Suggestions by the Cleveland Clinic reporters that other patients on the same product had problems did not hold up under closer scrutiny.

Case Report 2 (1987) - Carbamazepine

A letter published in The Lancet 6/20/87 from the Robert Wood Johnson Medical School in New Jersey reported on three anecdotal cases of patients who had been controlled on Tegretol (CIBA-Geigy) but went out of control when switched to generics. They were all reported to have regained control of seizures after the brand name product was reinstated.

An FDA investigation is in progress, and we have no data to report so far. It is worth noting, however, that CIBA has been putting a lot of pressure on state formulary committees lately in an effort to retain its share of the market in light of generic competition and the new Medicaid reimbursement rules. When CIBA changed its formulation and color a couple of years ago, the agency received some 50 ADR reports of therapeutic failures with the new tablet,

although it had been shown to be bioequivalent to the old formulation.

Case Report 3 (1984) - Tolazamide

A letter in Diabetes Care, January-February 1987, reports briefly on what appears to be a study of diabetic patients who were stabilized on Tolinase (Upjohn) and then switched to an unidentified generic (elsewhere identified as Zenith's). Fourteen of an unstated number of those initially observed allegedly suffered a loss of control of blood sugar levels. The observations were made in 1984 but not reported until some three years later. The letter, moreover, contains a number of disclaimers. A subsequent controlled study performed for Zenith and submitted recently to the agency allegedly failed to show any problem with the generic. We are currently analyzing that study.

Case Report 4 (1987) - Valproic Acid

A report to the PMA dated 8/20/87 reported on an incident in January 1987 in which an epileptic who had been stabilized on Depakene (Abbott) was given a generic (of unidentified manufacturer) and three days later had a seizure while driving. It is interesting that the reporter waited 8 months to report it, and then reported it to the PMA rather than to the company or to FDA. The first time FDA was made aware of the report was at the hearing in October. In addition to the lack of a responsible reporting history, this type of report is typical of anecdotal reporting, where there is an association made simply because a patient was switched to a generic and some adverse event happened. With millions of patients being switched and thousands of adverse events occurring at any given time, the probability that some of these switches will coincide with adverse events is high. FDA would normally not follow up on such a report. Neither would the manufacturer, whether brand name or generic. For the PMA to suggest to a Senate committee that such reports are significant seems to be stretching credibility.

Case Report 5 (1986) - Propranolol

This report comes via the PMA from Dr. O'Connor, who testified at FDA's Bioequivalence Hearing. It is anecdotal in nature, so its significance is questionable. In addition, it should be noted that Dr. O'Connor made many extravagant assertions at the hearing (e.g., that a patient went out of control on generic furosemide I.V.) and later failed to provide any material to FDA, despite repeated attempts. He also failed to cooperate with state officials investigating his allegations against unnamed pharmacists.

Dr. O'Connor submitted his report to the PMA over a year after the incident allegedly occurred. He claimed to report it to FDA in March of 1987, a year after the incident, but our system did not find the report.

Case Report 6 (1983) - Chlorpropamide

This was another delayed anecdotal report. The physician, who had not reported to FDA, related a case that occurred in 1983 of a diabetic patient who had been stabilized on 100-150 mg Diabinese (Pfizer) and was switched to an unnamed generic. She went out of control. Now, however, according to the report, she is stabilized on 350 mg of Diabinese. One is left to speculate whether she was on too low a dose of the drug when she went out of control, and that perhaps she would do just as well on 350 mg of the generic. No follow up is planned, because of the nature of the report and the long time interval. No report was made to FDA. The first we heard of the case was at the hearing, four years after the event.

Case Report 7 (1981 - 1982) - Furosemide

There seems to be a discrepancy between the dates given by Pfizer for the advent of the first generic furosemide and the dates of approval given in the Orange Book. Of the nine cases Pfizer and the PMA selected from the alleged 75 reports, six predate the first approval of a generic tablet. It is possible that these six reports involve unapproved products marketed by Premo and Pharmadyne, which were the subject of FDA legal action and on which we have no bioequivalence data. In any event, these reports and the three that could conceivably have been associated with approved generic products do not differ from many submitted to FDA regarding the brand name Lasix (Hoechst Roussel) product.

Case Report 8 (1987) - Methylphenidate

This is another anecdotal report that was not submitted to FDA. It allegedly involved a switch from the brand name Ritalin (CIBA-Geigy) to an unnamed generic product. It should be noted that this same physician reported the problem with valproic acid cited above. There is little we can do with such anecdotal reports except to add them to our system and to analyze for an unusual frequency. When such reports are not made to FDA, there is nothing we can do. Again, it is suspicious that this report was judged important enough to raise to a Senate committee but not important enough to bring to FDA's attention.

Case Report 9 (1987) - Carbamazepine, Phenytoin, Valproic Acid

This report refers to a "Medical Alert Bulletin" issued by the Epilepsy Institute of New York. FDA attempted to get more details of the alleged incidents with the drugs, but to no avail. The physician identified in the bulletin, Dr. Hart Peterson, failed to respond. However, there was some interesting facts uncovered by a reporter for Consumer Reports and published in the August 1987 issue (copy attached). It cites financial arrangements between the Institute and the three brand name drug firms. It also quotes Peterson as saying, "If I get any good solid cases and I could prove them, I certainly would. I personally haven't seen any really good cases where switching to a generic has caused problems."

Senator METZENBAUM. Our last witness is Jack Guildroy, American Association of Retired Persons, Washington, D.C.

Mr. Guildroy, you know that the roll call is on. We are happy to hear from you. Please come forward, but I think that as you are well aware, the Chair shares many of the concerns that the AARP has on this subject, and although we did not hear you first, I think your point of view has been spoken for so far.

But, please, can you take about 3 or 4 minutes before the five bells ring?

**STATEMENT OF JACK GUILDROY, AMERICAN ASSOCIATION OF
RETIRED PERSONS, WASHINGTON, DC**

Mr. GUILDROY. Thank you very much, Mr. Chairman. My name is Jack Guildroy. I am a member of the National Legislative Council of the American Association of Retired Persons, and with me is Judith Brown from our Public Policy Institute, who covers pharmaceutical issues for our Association.

We appreciate the Subcommittee's invitation to be here today. We are a membership organization representing about 27 million Americans age 50 and older. We commend you and other members of the subcommittee for focusing attention today on anticompetitive practices of some major pharmaceutical manufacturers to unfairly disparage the use of generic equivalents to their brand name products.

AARP has become increasingly alarmed at the flagrant scare tactics used by these companies threatened by generic competition since the enactment of the 1984 act. It is our members and other older Americans who are the primary victims of this campaign, since they are being frightened away from saving a great deal of money.

Efforts to persuade health professionals that generics are unsafe or ineffective have spawned a new kind of innovation in the drug industry. Early on, attempts to delay FDA approval for competing products, misleading ads in medical journals, letters sent to State formulary committees, doctors and pharmacists conveying false information were typical responses of companies faced with generic competition.

Later, however, the attacks intensified as anti-generic articles, TV interviews, misinformation from company salespeople took the place of earlier efforts because these newer tactics were generally outside FDA's regulatory reach.

Recent industry-sponsored methods to dissuade people from using generic drugs have been predictably successful in influencing public opinion about generics. In AARP's 1985 and 1986 national telephone surveys, we asked if respondents believed the Government holds the same standard for generic and name brand drugs alike.

In just one year, about ten percent of respondents shifted from agreeing that the government standards are the same into the "don't know" category. This translates into a 50-percent increase in the percentage of persons who are now confused and indeed do not know.

It is not at all surprising that doctors who have heard the same misleading messages for many years are increasingly reluctant to prescribe generics. After all, they are told is it not worth a few dollars to risk your patient's health?

Further, doctors have been informed that there exist high-risk patients, including the elderly, for whom generic substitution is especially dangerous. There is no evidence to support this theory, but the argument is presented in a logical and convincing manner in many forums.

We have been very vocal and visible in trying to counter this smear and fear campaign and expose the economic motives of those who unfairly disparage generics. Just a few of our recent efforts include articles in our widely circulated publications, "Modern Maturity," the AARP news bulletin, placement of FDA's document "Myths Versus Facts about Generic Drugs" in the New England Journal of Medicine last fall, and the production of a brochure for wide distribution to consumers using the same myths-versus-facts format.

Our efforts, however, are clearly not enough. We need the help of Congress to instruct the Administration to do more to set the record straight. We also call upon the concern, in its concern with the costs of health care in the United States, to closely monitor the untoward consequences of granting monopoly markets for essential drug products.

Given unreasonable price increases and uncompetitive activities evidenced in the pharmaceutical market, the nation may be left with the need to rethink the situation that protection by monopoly markets has created.

Thank you, Mr. Chairman.

Senator METZENBAUM. Thank you very much for your excellent statement, Mr. Guildroy. I have no questions because I agree with what you said.

Senator THURMOND.

Senator THURMOND. We are glad to have you with us.

Mr. GUILDROY. Thank you.

Senator THURMOND. How many members do you have in your organization?

Mr. GUILDROY. About 27 million members. You do not have to be retired to be a member, Senator Thurmond, just 50 or over, if you qualify.

Senator THURMOND. Well, I guess I could qualify in either event. [Laughter.]

Are you aware of the instances cited by Mr. Mossinghoff in which patients who had switched from brand name drugs to generic drugs allegedly suffered adverse reactions, and would you comment on their significance?

Mr. GUILDROY. Well, we know about the allegation, but may I ask Judith Brown to respond to that?

Senator THURMOND. Ms. Brown, we are glad to hear from you.

Ms. BROWN. Thank you. We are aware of every instance that—

Senator THURMOND. Speak louder.

Ms. BROWN. We are aware of every instance that the pharmaceutical manufacturers have brought up to demonstrate that generic equivalents are somehow ineffective or unsafe, and we have relied

upon FDA's very close examination of the facts in each case they have brought up—the FDA has found no evidence.

We are getting, frankly, a little tired of the expenditure of resources that has to go into the examination of every individual case and all the scariness that is involved in each case. We certainly want FDA to scrutinize every allegation they receive, but we are very tired of them all proving to be unfounded.

Senator THURMOND. And you feel safe in relying on the FDA, I presume.

Ms. BROWN. Very safe.

Senator THURMOND. I see. Thank you very much.

Senator METZENBAUM. Thank you very much.

[Statement follows:]



Testimony
of the
American Association of Retired Persons
before the
Subcommittee on Antitrust, Monopolies and Business Rights
on
Competitive Problems in the
Pharmaceutical Drug Industry

U.S. Senate
October 21, 1987

The American Association of Retired Persons (AARP) appreciates the Subcommittee's invitation to be here today. AARP is a membership organization representing over 27 million Americans age 50 and older. AARP has always maintained a keen interest in pharmaceutical issues since older persons consume a disproportionately high amount of prescription drugs. Although those age 65 and older constitute 12% of the population, they consume 30% of the nation's prescription drugs. AARP's interest in the pharmaceutical arena is on access to safe, effective and affordable drugs.

We commend you, Senator Metzenbaum, and other members of the Subcommittee, for focusing attention today on anticompetitive practices of a few major pharmaceutical manufacturers such as disparaging the use of generic equivalents to their brand name products.

AARP has become increasingly alarmed at the flagrant scare tactics used by those companies threatened by generic competition since the enactment of the 1984 Drug Price Competition and Patent Term Restoration Act. Older Americans are the primary victims of this campaign since the major difference between a brand and a generic equivalent is the difference which comes out of older persons' pocketbooks.

Our formal statement discusses three areas in depth:

- o Industry practices of disparaging generic competition.
- o Effects of the anti-generic campaign.
- o AARP's efforts to counter misinformation.

Industry Practices

Efforts to persuade health professionals that generics are unsafe and/or ineffective have spawned a new realm of "innovation" in the drug industry. Soon after the 1984 law was passed, certain pharmaceutical companies who had enjoyed a monopoly market for products like Inderal and Valium for more than 20 years sought to extend their monopolies even further by petitioning the FDA to delay approval of generic equivalents. These "citizens petitions" to change long-established testing requirements were filed by numerous manufacturers to require that FDA apply more stringent test standards for the generic competitors than even the brand-name product had undergone. This had the effect of delaying generic competition while the FDA considered each petition for possible scientific merit. But FDA found none. Further, it was the same FDA staffers who were charged with both jobs of reviewing the petitions and reviewing generic applications, and obviously could not perform both functions at once. Even if the companies succeeded in delaying generic approvals by a few weeks, their gain was considerable: several brand name products had sales of over \$1 million per day.

Misleading advertisements started appearing in medical journals and company letters were mailed to doctors and pharmacists about products like Mellaril to dissuade health professionals from using generics. State formulary committees received supposedly independent letters from doctors (that were clearly generated from the company) insisting that generic copies of brands like Diabinese be kept off state formularies. We cite these two products as examples because, although there have been many similar infringements, both of these actions resulted in strong letters being issued from FDA to the companies involved, ordering them to cease and desist.

Articles that appeared in consumer magazines and letters to the editors of newspapers that were strongly influenced by industry were harder for FDA to react to since they were not officially sponsored by the companies and therefore out of reach of FDA's regulatory authority.

Other anti-generic tactics that are beyond FDA's reach involve supposedly independent scientific research and exhibits on display at conferences held across the nation for health professionals. At one such meeting of the American Psychiatric Association here in Washington, AARP staff toured the exhibits and found that gross misrepresentations about generics were the rule, not the exception, in the pharmaceutical exhibit hall.

In the scientific research display area, which was set apart from company promotional booths, researchers shared their supposedly "unbiased" data showing brand product superiority over the generic, but neglected to hide the company shipping labels that were pasted to cartons of their "independent" studies. At another research display, the researcher manning the exhibit which was purportedly from an academic institution was actually wearing a company badge with his name imprinted on it. The exhibit, of course, touted study findings that generics acted differently from the company's brand product.

Salespersons from various company promotional booths confided that "The FDA doesn't like us to say this, but..." and "We've done our own informal study..." followed by false statements about their products' supposed superiority over generics. Many salespersons provided damaging misinformation about the FDA approval standards for generics as compared their brand products - more than one sales representative went so far in their distortion of the $\pm 20\%$ rule that they stated that their brand products were 120% bioavailable to the body. This is quite a feat, considering that 100% bioavailability cannot be exceeded.

A long running series of articles raising false fears about generic substitution appeared in a medical-news tabloid that is mailed free to 150,000 doctors. The tabloid, "Medical Tribune," is supported by brand industry advertising and had been published

by the owner of a public relations firm specializing in brand industry advertising. Their crusade against generics was intense and unfounded.

An increasingly popular arena for anti-generic propaganda has been state legislatures. Early in 1985, New York state legislators were so inundated with misrepresentations from major pharmaceutical companies that they called upon Representative Henry Waxman, the co-sponsor of the 1984 law, to provide some guidance as to the new law's provisions to assure generic safety and efficacy. These blatant misrepresentations are particularly onerous when they occur during states' consideration of programs to assist near poor elderly persons in paying for their prescription drug bills, as was the case in New York.

In other state capitols, AARP has encountered debates with industry-sponsored advocates who, in one case, informed the audience that generic drug companies can "mix active ingredients with cement."

Through their long-standing campaign against generics, Ayerst Laboratories has singled themselves out by the scope and duration of their activities to protect their top selling product, Inderal. Ayerst has given "educational grants" to several organizations such as the California-based Pharmacists Planning Service, Inc. and a group formed at the Philadelphia College of

Pharmacy entitled C.U.R.E.P. (Committee for the Understanding of Research in Ethical Pharmaceuticals). Both organizations engaged in activities to raise fears in the minds of health professionals about the consequences of substituting generics for brand products.

Ayerst also has been the covert sponsor of supposedly "independent" academicians and practitioners who go on the speaking circuit to cast false aspersions on the safety and quality of generic drugs. The media tours have resulted in newspaper articles with headlines such as "Warning Sounded on Generic Drugs." A nationally syndicated TV show this January promised viewers throughout the day and in the TV Guide that they would be learning of the "Dangers of Generic Drugs." The effect of these and countless other articles and TV shows has been intense and far-reaching.

Effects of Anti-generic Campaign

Recent industry-sponsored methods to dissuade people from using generic drugs have been predictably successful in influencing public opinion about generics. In AARP's 1985 and 1986 national telephone surveys, we asked if respondents believed the government holds the same standards for safety, effectiveness and

quality for both generic and name brand drugs. In just one year, about 10% of respondents shifted from agreeing that government standards are the same into the "Don't Know" category. This translates into a 50% increase in the percentage of persons who are now confused and, indeed, "don't know".

As taxpayers, we all pay more unnecessarily for brand drugs through the state Medicaid programs. State formulary committees, which make determinations about which drug products will be reimbursed by the state, are the frequent targets of anti-generic messages. It is often the case that personal contacts and brand name salesmanship are operating in these committees instead of scientific judgments. Many state formulary committees serve only to delay or deny access to generics in their states.

Industry lobbying and misinformation has also kept generic incentives at minimal levels in the few existing state programs to assist the elderly in paying for their critical prescription drugs. A similar scenario developed in the U.S. House of Representatives this July when an amendment was introduced to thwart generic drug substitution under the proposed Medicare catastrophic health insurance plan.

It is not at all surprising that doctors, who have heard the same misleading messages for many years, are increasingly reluctant to prescribe generics. After all, they are told, is it worth a

few dollars to risk your patients' health? Further, doctors have been informed that there exist "high risk" patients, which include the elderly, for which generic substitution is especially dangerous. There is no evidence to support this theory, but the argument is presented in a logical and convincing manner in many forums.

AARP's Efforts to Counter Misinformation

It is unfortunate that the primary victims of this widespread campaign to disparage generics are older Americans. They not only consume more drugs, especially for chronic conditions, but they pay a larger percentage of drug costs directly when compared to other segments of the population. They often must pay for these non-discretionary items from limited incomes. A 1985 study conducted for AARP showed prescription drugs to be the second-highest out-of-pocket health expense for older Americans, behind long term care. In 1986, it was estimated that the age 65 and over population spent \$9 billion on prescription drugs, with \$7.3 billion (81%) being paid out-of-pocket.

The skyrocketing costs of single-source prescription drugs since 1981 have made it imperative that consumers save money where they can. There has been no alternative when companies like Smith Kline raise the price of a top-selling drug like Dyazide 31% in one year. But when industry profits from excessive price increases go to fund tactics to frighten people away from the

competing generic products when they finally become available, we believe their actions are unconscionable.

It is for these reasons that AARP has been very vocal and visible in trying to counter the "smear and fear" campaign and expose the economic motives of those who disparage generic equivalents. Our recent efforts include:

- o July 1985 - Congressional testimony on drug price increases and anti-generic activities at House Subcommittee on Health and the Environment hearing.
- o December 1985 - Article in AARP's Modern Maturity magazine "Drug Campaign Draws Fire", informing our members that the controversy is based on economics, not science.
- o February 1986 - Speech to Congressional staff and Pharmaceutical Manufacturers Association, "Pharmaceutical Industry and the Consumer: Renewing the Trust", calling for an end to anticompetitive industry practices against generics.
- o April 1986 - Modern Maturity TV Show, "Drug Wars".
- o April 1986 - AARP Newsbulletin article, "Drug Scare Tactics Misinform Consumers".
- o May 1986 - AARP Highlights article, "Generic Drugs".
- o September 1986 - AARP Newsbulletin article, "Don't Believe the Fear and Smear' Anti-generic Campaign".

- o October 1986 - AARP sponsored reprint of FDA's document "Myths vs. Facts About Generic Drugs" in three issues of the New England Journal of Medicine. Thousands of reprints were mailed to doctors who filled out coupons requesting copies for themselves and their patients.
- o Fall 1986 - "Where We Stand on Generic Drugs," an AARP Office of Communications publication.
- o April 1987 - Congressional testimony on drug price increases and anti-generic activities for House Subcommittee on Health and the Environment hearing.
- o October 1987 - AARP Newsbulletin article "Generic Drug Wars: Consumer Activists Challenge Industry Whispering Campaign Against Generics".
- o October 1987 Consumer Video sent to 200 TV Stations "A Consumer Report on Generic Drugs," featuring FDA Commissioner Young and Representative Henry Waxman. So far, the video has reached 30 million households.
- o Fall 1987 - Brochure printed of a consumer version of FDA's document "Myths vs. Facts About Generic Drugs" an AARP Public Policy Institute publication for widespread distribution to AARP members and others.
- o Numerous speeches and media interviews by AARP staff and Executive Director, Cyril Brickfield, to expose the anti-generic campaign.

Recommendations

Although AARP has tried to counter-attack the brand industry's tactics, our efforts are clearly not enough. We need the help of Congress to instruct the Administration to do more to set the record straight. Further, we need FDA to act quickly to make sure that generic copies of very old brand drugs undergo current state of the art tests that may not have been available at the time of the drug's approval years ago. In this way, doctors and pharmacists will be assured that any generic drug that has been approved by the FDA has undergone the most current bioavailability or dissolution testing and is interchangeable with the reference product. As it exists now, the generic products which are not considered by FDA to be interchangeable only serve to confuse the marketplace. Therefore, AARP recommends the elimination of all "B-rated" generics where the state of the art is available to ensure the products' bioequivalence.

AARP also calls upon the Congress, in its concern with the costs of health care in the United States, to closely monitor the untoward consequences of granting monopoly markets for essential drug products. Given unreasonable price increases and uncompetitive activities evidenced in the pharmaceutical market, the nation may be left with the necessity to rethink the situation that extended monopoly protection has set up.

Conclusion

We had hoped that the 3-day conference on bioequivalence held in Washington, D.C. last fall by the FDA and widely attended by all facets of the pharmaceutical community would put the anti-generic campaign to rest. It was an opportunity for anyone to come forward with any scientific data to show that there were problems in the FDA approval process for generics or that there were problems in actual medical practice using generic equivalents. Not one shred of evidence emerged to show that any problems exist with the generic drugs that FDA has approved as bioequivalent to their brand name counterparts. FDA Commissioner Frank Young presided over the conference and closed the formal hearing by saying "I find sophomoric the concept, 'Well, it's out there but we don't know.' That doesn't cut any ice. I think you really have to approach it with a scientific analysis indicating how you develop a hypothesis and test it... the lack of serious experimental data presented here was a surprise to me."

Dr. Robert Temple, Director of FDA's Office of Drug Research and Review, made perhaps the most astute comment: "... in a world where I presume there is a vigorous if not desperate search for examples of bio-inequivalence ...it seems to me that if they were out there and obvious, we should have seen them by now."



American Association of Retired Persons

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Fall 1987

Generic Drugs



Myths vs. Facts

Information from the
U.S. Food and Drug
Administration



Myths vs. Facts About Generic Drugs



"Generic drugs" is the term for prescription drugs that are the same as brand-name drugs. As with any new type of product, most brand-name prescription drugs are developed under a patent. This patent serves to protect a drug firm's investment in developing the drug by giving the company the sole right to sell the drug while the patent is in effect. Thus, generic versions of that drug may be sold by competing drug companies only after the patent expires — generally about 17 years after the original drug was discovered.

Because competition enters the picture when a patent expires, generic drugs usually sell for less than the brand-name product from the original manufacturer. The fact that generics generally sell for less has led many people to believe that generics are in some way inferior to brand-name products. That's not true; generic drugs contain exactly the same active ingredients as the brand-name drug and must be just as safe and effective.

Here's some more information to clarify the record on generic drugs:

Myth: A new law, enacted in 1984, permits the Food and Drug Administration to ignore safety and effectiveness requirements for generic drugs while brand-name drugs still must meet these rigid tests.

Fact: The new law, the 1984 Drug Price Competition and Patent Restoration Act, does **not** lower any standards for generic drugs. Previously, generic manufacturers had to perform their own tests to prove that the active ingredients in their products were safe and effective. But since that had already been proven when the equivalent brand-name drug was first marketed by the original manufacturer, there was really no need to test all over again. However, generic drugs must go through scientific testing to show that they work just as well as the original drug. Although the law is new, generic drugs are not. They've been around for many years. The new law just makes them available for many more drugs.

Myth: Generic drugs just won't do the job as well as brand-name drugs.

Fact: Under the law, generic drugs must be bioequivalent to their brand-name counterparts to gain FDA approval. This means that the generics must contain the same active ingredients and must be identical in strength, dosage form (tablet, solution, etc.), and route of administration (for example, taken by mouth or through injection). Further, they must release the same amount of drug into the body as the brand-name drug.



Myth: Generics take longer to act in the body.

Fact: In seeking FDA approval for their products, generic manufacturers must submit evidence that their drugs will have the same therapeutic effect as the brand-name counterparts. This means that a generic product can be expected to deliver to the bloodstream, or other site where the drug does its work, the same amount of active ingredient as the original product.

Myth: Generic drugs are not as potent as brand-name drugs.

Fact: Generic drug manufacturers have to ensure that their products are of the same quality, strength, purity, and stability as the brand-name products.



Myth: Generics are not as safe as brand-name drugs.

Fact: FDA requires that *all* drug products be safe and effective. Since generics use the same active ingredients as their brand-name counterparts and work the same way in the body, generics are as safe and effective as their brand-name equivalents.



Myth: FDA requires that brand-name manufacturers test new drugs in thousands of patients, but it lets generic firms get by with tests in only 20 or 30 healthy volunteers.

Fact: Generic drugs are duplicates of products that have already been tested for safety and effectiveness. Therefore, generic manufacturers need only prove to FDA that a drug behaves the same way in the body as the original version. This requires only small-scale tests. In fact, the same small-scale testing is done for brand-name drugs whenever they are reformulated.

Myth: Generic manufacturers only have to prove that the active ingredients in their products get to the bloodstream. That doesn't mean that their products are used by the body in the same way.

Fact: When the same amount of the active ingredients of the generic version get into the bloodstream at the same rate and to the same extent as the brand-name version, there is no scientific reason to believe that the effects of the two drugs will differ.



Myth: Most drugs are tested for bioequivalence in healthy young volunteers, yet 25 percent of all prescription drugs are taken by the elderly who don't react the same to drugs.

Fact: While the elderly may often absorb and process (metabolize) drugs differently than younger people, there is no proof that drugs will perform differently in older persons. Further, it isn't ethical to force (possibly) weakened or disabled patients to give blood samples and face the other discomforts of bioequivalence testing. Further, such patients cannot be used in bioequivalence testing because they are usually taking other drugs concurrently.

Myth: Brand-name drugs are manufactured in modern facilities while generics are often manufactured in substandard facilities. Thus, generics are generally inferior.

Fact: FDA allows no drugs to be manufactured in substandard facilities. FDA officials inspect more than 5,000 drug plants a year to ensure that standards are met. Generic firms have state-of-the-art plants that compare favorably with those of brand-name firms. (In fact, brand-name firms account for an estimated 70 to 80 percent of generic drug production, making duplicate versions of their own or other companies' brand-name drugs, but selling them without the brand name.)



Myth: Patients using generic products are more likely to suffer side effects than those using brand-name drugs.

Fact: There is no evidence of this. FDA monitors reports from doctors and others of adverse drug reactions and has found no difference in the rates of adverse reactions between generic and brand-name drugs.

Senator METZENBAUM. Before I conclude the hearing, I just want to say publicly how much I appreciate the ranking member spending the entire morning with us. I think it indicates his concern for the problems that have been addressed in this hearing. I want to thank you publicly for doing so. I want to thank the witnesses, and that concludes our hearing.

Senator THURMOND. I want to congratulate you for the fair manner in which you held it.

Senator METZENBAUM. Thank you very much.

[Whereupon, at 12:14 p.m., the subcommittee was adjourned.]

[The following miscellaneous material was subsequently supplied for the record:]

Questions submitted by Senator Metzenbaum to Ayerst Laboratories

1. One topic discussed extensively at the October 21 hearing was the Ayerst program that awards physicians "points" for prescribing Inderal LA and filling out a marketing survey. To how many physicians was this program offered? How were such physicians contacted? Please provide the Subcommittee with a copy of the promotional material distributed to these physicians. How many points have been awarded under this program? How many of these points have been converted into airplane tickets or other tangible benefits? By how many physicians? Does Ayerst have any other similar programs for other Ayerst products? Please provide the Subcommittee with a copy of the marketing survey required for the Inderal LA program.

2. What non-medical inducements, other than the programs discussed in the question above, does Ayerst offer physicians to encourage the prescription of Ayerst products? Please describe each fully.

3. Another topic discussed at the hearing was the use of public relations firms to set up media tours in which health care professionals suggested that use of generic drugs could present health risks. In the last 3 years, approximately how many such media tours have Ayerst directly or indirectly sponsored? Please provide the names of the public relations firms employed to coordinate or promote these tours, and the approximate amount of money paid to these firms for such activities. Please provide the total number of health care professionals serving as spokespersons on these media tours and the total amount of money paid to such spokespersons.

4. How much did Ayerst spend to sponsor the study reported in the November 14, 1986 Journal of the American Medical Association comparing the cost of generic and name brand drugs? How much did Ayerst spend through the use of public relations firms or otherwise to promote or advertise the "results" of that study?

5. In the last 3 years, what funds if any has Ayerst Laboratories provided to the following: Pharmacy Planning Service; Philadelphia College of Pharmacy and Science; Center for the Study of Drug Development; Medicine in the Public Interest; Asthma and Allergy Foundation; Louis Lasagna; or Fred Mayer. For what purpose were such funds provided? Please describe fully the relationship of Ayerst to these entities and provide a copy of any funding or grant agreement involving Ayerst and any of these entities. In addition, please provide a copy of any other document that incorporates or references any agreement between Ayerst and any of these entities involving generic drugs.

Ayerst**AYERST LABORATORIES**

DIVISION OF AMERICAN HOME PRODUCTS CORPORATION

685 Third Avenue New York, N.Y. 10017-4071 Tel. (212) 878-5900 / Cable ALPHAMIN, New York

January 13, 1988

Senator Howard M. Metzenbaum
United States Senate
Committee on the Judiciary
Washington, D.C. 20510-6275

Dear Senator Metzenbaum:

This is in response to your letter of November 17, 1987, in which you asked Ayerst Laboratories to answer several questions in connection with a hearing of the Subcommittee on Antitrust, Monopolies and Business Rights. We have answered the questions raised on the above referenced letter in the order asked.

1. The program to which you refer is the Inderal LA patient profile program. In this program, information was sought about the patient population for whom Inderal LA therapy was being initiated with the expectation of developing future marketing and educational programs. Approximately 30,000 physicians were asked to prepare and submit patient-profile information concerning patients whom they believed would benefit from Inderal LA treatment. In return for these efforts physicians were credited with points for each profile they provided, as an honorarium.

Once a number of points had been credited to the physician, these could be exchanged, at his/her option, for medical texts, diagnostic equipment, or travel certificates intended to facilitate attendance at medical meetings identified in supplemental program material.

The physicians were contacted in person by Ayerst representatives during the course of regular sales calls. After identifying those physicians who were already using, or had expressed an intention to use, Inderal LA, they were given copies of the descriptive information that is submitted as Attachment A to this letter. The Attachment also includes a copy of the questionnaire that the physicians were requested to complete.

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As of November 30, 1987, a total of 504,120 profiles had been submitted by participating physicians and approximately 721 physicians received travel certificates, texts or diagnostic materials. It is anticipated that as the program draws to a close, additional physicians will be receiving awards. Ayerst does not have any similar programs in effect at this time.

2. As indicated in response to the preceding question, Ayerst does not regard the Inderal LA patient profile program as an "inducement" to encourage the prescription of the product. Nor does Ayerst offer other items or payments to physicians in exchange for prescriptions. The company does, of course, make sales calls to physicians, and, in connection with such calls, it leaves pads, educational materials, etc., with the physicians, as is customary in the pharmaceutical industry. Such reminder items are merely designed to keep Ayerst's name in the mind of the physician.

3. In recent years, there has been considerable debate concerning the pros and cons of generic substitution. As a major supplier of branded pharmaceuticals, Ayerst has an interest in providing opportunities for health-care professionals who share Ayerst's views to air their opinions. Therefore, Ayerst has asked professionals who have expressed opinions similar to Ayerst's if they would be willing to state their views publicly, and some have indicated a desire to do so.

During the past three years, Ayerst has organized four programs that were designed to provide opportunities for health-care professionals to express their views to the public. In each program, Ayerst's public relations firms (either Edelman or Burson Marsteller) have been asked to arrange for media appearances on talk shows, newscasts, interviews by newspapers, etc. The interested professionals were then asked if they would be willing to speak in these forums.

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Over the three year period, approximately 20 health care professionals participated in the media programs identified above. For each appearance, Ayerst reimbursed their itemized expenses (travel, lodging and meals) and also granted an honorarium in the range of \$1,000 to \$1,500 to compensate them for their travel time and time loss from their practice or professional activities. Ayerst estimates that the total amount paid to the health-care professionals in connection with these programs, including reimbursement for itemized expenses, was approximately \$710,000 for the three year period. Ayerst estimates that it paid approximately \$350,000 to its public relations firms to arrange and coordinate these media programs, and an additional \$440,000 for all associated out-of-pocket agency expenses over the three year period. The total spent by Ayerst during this three year period on these public relations efforts were less than .01 of its sales during this same period.

4. Ayerst sponsored this study, which was conducted by the Leonard Davis Institute, under a grant totalling \$51,500. Ayerst expended approximately \$90,000 to publicize the results of the report through its public relations firms. These monies were part of the monies expended on public relations efforts referred to in response to question three above.

5. We are unaware of any grants or other funds by Ayerst that have been provided in the past three years to the persons and organizations listed in your letter other than to Pharmacists Planning Service, Inc., (PPS), which is an educational, nonprofit organization of California pharmacists and to the Philadelphia College of Pharmacy and Science. A \$10,000 open grant was provided by Ayerst to PPS in October 1985 to support its educational programs while a \$15,000 grant was paid to the Philadelphia College of Pharmacy through one of our public relations firms to assist in their sponsorship of one of their educational programs. Ayerst does not have any formal relationship with any of the listed persons or organizations and does not have any funding agreements, grant agreements or agreements involving generic drugs with them.

Sincerely,



Arnold Somin
Executive Vice-President
Ayerst Laboratories



APhA

American
Pharmaceutical
Association

John F. Schlegel, PharmD
President

2215 Constitution Avenue, NW
Washington, DC 20037
(202) 628-4410

D. Stephen Crawford
Chairman of the Board

The National Professional Society of Pharmacists

November 5, 1987

The Honorable Howard Metzenbaum
Chairman
Senate Subcommittee on Antitrust,
Monopolies and Business Rights
308 Senate Hart Office Building
Washington, DC 20510

Dear Mr. Chairman:

The American Pharmaceutical Association (APhA) is pleased to add our comments to the record of the hearing on anti-generic pharmaceutical marketing practices which you chaired October 21, 1987. APhA is the national professional society of pharmacists, representing the third largest health profession in the country.

The committee has raised legitimate concerns about pharmaceutical marketing practices, and as the professionals responsible for drug use control, we share your concerns. APhA has a strong and consistent record in favor of making generic drug products available to the public. In 1969, APhA launched the effort to introduce drug product selection laws in all fifty states. Such laws reestablished the pharmacist's authority for making drug product selection decisions pursuant to a physician's prescription order.

We continue to believe that the public should have access to quality generic pharmaceuticals when available. The availability of generic drug products in the marketplace produces several positive outcomes. Such availability:

- o Stimulates healthy competition among the manufacturers;
- o Allows the consumer to play a more active role in selecting his or her health care products;
- o Promotes cost effective quality health care; and
- o Reduces the overall cost burden on the public, the government and other third party payors who are purchasing prescription drug products.

APhA supports the efforts of FDA and its Bioequivalency Division to ensure that only quality generic drug products are approved. Although some authors have stated that the FDA guideline allows up to a 40% difference in bioavailability between products in the market place, FDA reports that the actual difference between generic product and reference

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product averages 3.5%. This is well below the allowable lot-to-lot variation of most innovator products. The large lot-to-lot variation for brand name products can be more significant than variations among generics. A dramatic example of large lot-to-lot variation recently occurred with a particular diuretic drug. The innovator manufacturer had to supply the FDA with a single lot of the drug to use as the standard for bioequivalency testing of generic products because the large lot-to-lot variation in the brand product would have obscured any difference between the brand and a generic product.

It has been argued that patients should not be switched to generic drug products because of the dangers of toxicity or sub-therapeutic drug levels experienced with certain drugs. The pharmacists within FDA are well aware of those products which require special consideration because of a narrow therapeutic index or because of bioavailability problems with the innovator product. The FDA's Orange Book reflects that understanding in its listing of digoxin and phenytoin for example.

Likewise, pharmacists practicing in community and hospital settings have a thorough knowledge of the parameters which must be considered when performing drug product selection in response to a prescription order. All pharmacists spend a minimum of five years in college studying and mastering topics such as how drug products are formulated, how solid drugs dissolve and are dispersed within the body, how drugs exert their therapeutic action, and how drug products are eliminated from the body. No other group of health professionals has the same degree of educational training nor practical day to day experience with both brand and generic drug products as pharmacists. While we do believe that there are a few cases where a physician may determine that a patient must be maintained on a particular brand or generic drug product, in the great majority of cases, pharmacists are in the best position to make drug product selection decisions pursuant to a prescription order.

There have been multiple examples of innovator manufacturer advertisements which unjustly attack the quality of generic drug products. One company's "Dear Pharmacist" letters about an antipsychotic drug stated that the company had received a number of inquiries and implied that problems would exist due to the substitution of a generic. Another company's "Dear Doctor" letter on its oral antidiabetic product is another attempt at suggesting that generic products are inferior. FDA formally objected to both of these letters and forced the first company to correct the implication left by its letter. These and many other similar specific examples should be on file at the FDA.

There have been very aggressive advertisements placed in medical journals by brand name manufacturers. A good example is the ad for a particular heart drug which appeared in the New England Journal of Medicine. It stated that generic drug products did not necessarily have a place in the treatment of serious diseases and urged physicians to write "do not

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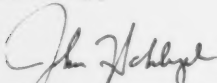
substitute" on their prescription orders. APhA supports the pharmaceutical industry's right to promote its products to health care professionals, but we feel that the promotion should be based on good scientific information, not half-truths and scare tactics.

The United States has a pharmaceutical development and distribution system that is the envy of the world. Clearly, this system is designed to rely on each party to perform a role in which it owns the dominant expertise: pharmaceutical manufacturers to develop and produce drugs, the FDA to approve and control drugs, the physician to prescribe drug therapy, and the pharmacist to select drug products pursuant to a prescription order and to monitor and counsel patients. The system as described is designed for success. When any one party is allowed to step outside of its area of expertise and inhibit the actions of another party in the system, the quality of drug therapy and overall health care is unnecessarily diminished.

Clearly, some pharmaceutical manufacturers have used the emotional rather than scientific marketing approach in an attempt to deter pharmacists from exercising their professional judgment in drug product selection. We encourage the committee to use its influence to assist our profession in urging manufacturers to promote their products based on scientific data.

We appreciate the opportunity to make our position known. Should you wish further clarification, we would be happy to meet with you or your staff.

Sincerely,



John F. Schlegel, Pharm.D.
President

JFS/hjp

